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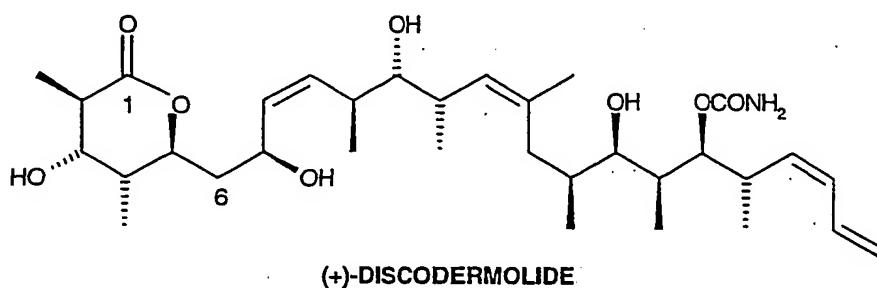
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(54) Title: PROCESS FOR PREPARING INTERMEDIATES FOR THE MANUFACTURE OF DISCODERMOLIDE AND DISCODERMOLIDE ANALOGUES

(57) Abstract: The invention relates to a process for the preparation of a substituted alkene of formula (I) wherein R₁, R₂ and R₃ are independently of each other a protecting group for a hydroxy group or hydrogen and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, which alkene constitutes an intermediate for the preparation of discodermolide and discodermolide analogues.

Process for Preparing Intermediates for the Manufacture of Discodermolide and Discodermolide Analogues

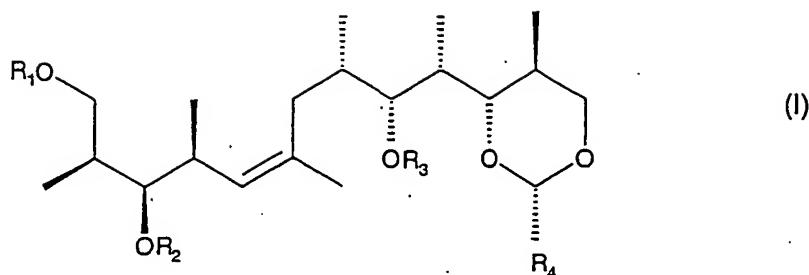
The invention relates to a process for preparing intermediates for the manufacture of discodermolide and discodermolide analogues and to the intermediates obtained during the process.



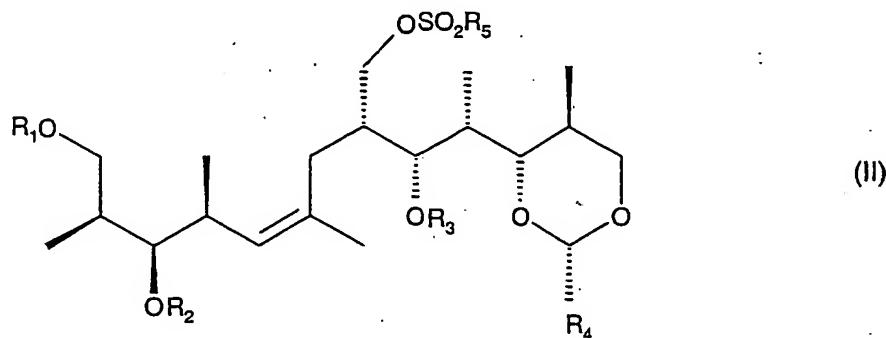
(+)-Discodermolide is a polyketide natural product that was isolated from extracts of the marine sponge *Discodermolide dissoluta* by researchers at the Harbor Branch Oceanographic Institution [S.P. Gunasekera et al., J. Org. Chem. 1990;55:4912-15 (published erratum appears in J. Org. Chem. 1991;56:1346)]. Discodermolide lacks obvious structural resemblance to paclitaxel, yet it shares with paclitaxel (the active substance in the drug Taxol®) the ability to stabilize microtubules. Paclitaxel has proven to be useful in treating some types of cancer in clinical practice. Discodermolide binds to tubulin competitively with paclitaxel and was shown to have utility against hyperproliferative disorders (see, e.g., WO 97/20835). Future development of discodermolide or structurally related analogues is hindered by the lack of a natural source that could provide greater amounts of the compound, since naturally occurring discodermolide is scarce and harvesting the producing organism presents logistical problems. Also lacking is a feasible synthetic route. Accordingly, there is a need for improved processes of manufacture of discodermolide and analogues hereof and for novel intermediates for such processes of manufacture which processes and intermediates enable the manufacture of commercially acceptable quantities of discodermolide and structurally related analogues.

The present invention relates to a process for preparing a substituted alkene of formula I

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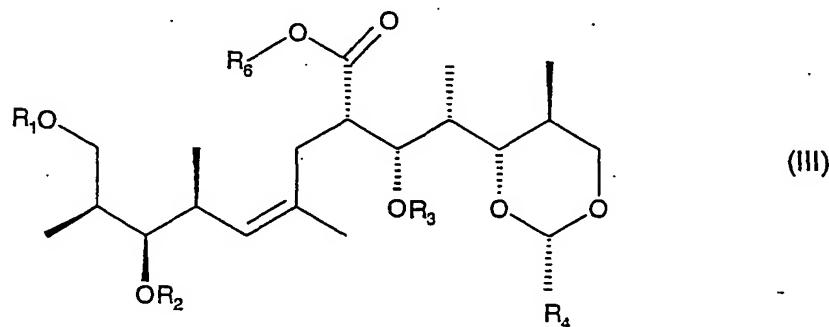
wherein R₁, R₂ and R₃ are independently of each other a protecting group for a hydroxy group or hydrogen and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, in which process a sulfonate of formula (II)



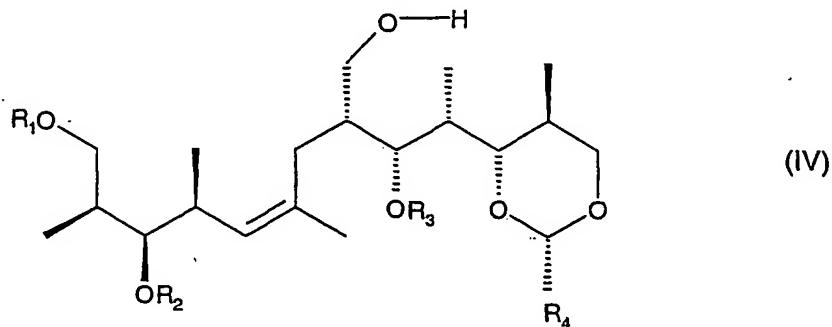
wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different, R₄ has the meaning as defined for the compound of formula I and R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, is reduced, e.g., by treatment with NaBH₄, LiBH₄, diisobutyl aluminium hydride, LiB(ethyl)₃H, Zn, tributyl tin hydride or, preferably, LiAlH₄, and afterwards, if desired, one, two or all protecting groups R₁, R₂ and R₃, in particular the protecting group R₁, are detached. Suitable reaction conditions for a reduction utilising LiAlH₄ are, for example, described in J. Org. Chem. 1980, 45, 2550 to 2551 or also J. Am. Chem. Soc. 1951, 73, on page 2874 (second Example described there). NaBH₄ can, for example, generally be employed in dimethyl sulfoxide or sulfolane at a temperature between 15 °C and 100 °C, e.g. 25 °C or 85 °C, and tributyl tin hydride generally in refluxing 1,2-dimethoxyethane (DME) in the presence of sodium iodide.

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Furthermore, the present invention relates to a process for preparing a substituted alkene of formula I wherein R_1 , R_2 and R_3 are independently of each other a protecting group for a hydroxy group or hydrogen and R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, in which process the carboxylic ester of the formula III



wherein R_1 , R_2 and R_3 are all protecting groups for a hydroxy group which protecting groups can be identical or different, R_6 is alkyl or arylalkyl, and R_4 has the meaning as defined for the compound of formula I, is first reduced, e.g., by treatment with LiAlH_4 , the obtained alcohol of the formula IV



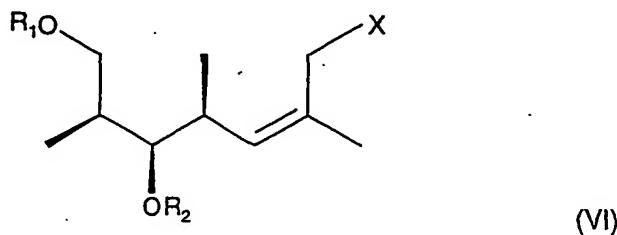
wherein R_1 , R_2 , R_3 and R_4 have the meanings as defined above for the compound of formula III, is further reacted with a compound of formula V



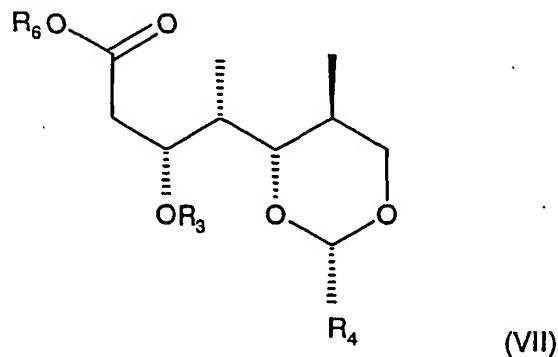
wherein R_5 is alkyl or aryl which is unsubstituted or substituted by alkyl, and Hal represent halogen under reaction conditions known as such and the obtained sulfonate of formula II

wherein R₁, R₂, R₃ and R₄ have the meanings as defined for the carboxylic ester of formula III and R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, is further reduced, e.g., by treatment with LiAlH₄, and, if desired, one, two or all protecting groups R₁, R₂ and R₃ are detached by methods known in the art.

Additionally, the present invention relates to a process for preparing a carboxylic ester of formula III wherein R₁ and R₂ are protecting groups for a hydroxy group which protecting groups can be identical or different, R₃ is hydrogen, R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R₆ is alkyl or arylalkyl, in which process an allyl halide of the formula VI



wherein R₁ and R₂ have the meanings as defined for a carboxylic ester of formula III and X is halogen, preferably bromine or iodine, is reacted with a carboxylic ester of formula VII



wherein R₃, R₄ and R₆ have the meanings as defined for a carboxylic ester of formula III in the presence of a base.

The invention also especially relates to a sulfonate of formula II wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different,

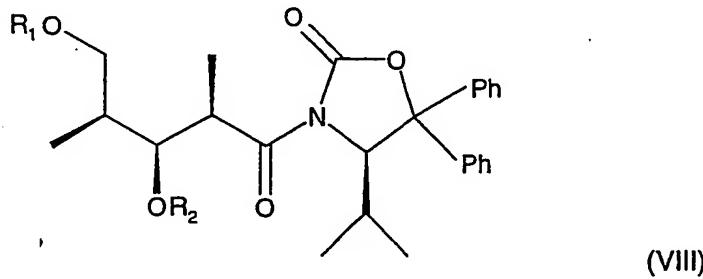
R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, preferably mono- substituted by alkoxy, and R_5 is alkyl or aryl which is unsubstituted or substituted by alkyl and to the synthesis of such sulfonate. Preferably in such sulfonate of formula II, R_1 and R_2 are identical, R_1 , R_2 and R_3 are benzyl or silyl protecting groups, and R_5 is lower alkyl or phenyl which is substituted, most preferably monosubstituted, by lower alkyl. In a very preferred embodiment, R_1 and R_2 and R_3 are all *tert*-butyl dimethylsilyl, R_4 is phenyl which is unsubstituted or monosubstituted by methoxy and R_5 is methyl or phenyl which is monosubstituted by lower alkyl.

Furthermore, the invention especially relates to a carboxylic ester of formula III wherein R_1 and R_2 are protecting groups for a hydroxy group which protecting groups can be identical or different, R_3 is a protecting group for a hydroxy group or hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl. In a preferred embodiment of the invention, the carboxylic ester of formula III comprises radicals R_1 and R_2 , which are identical, R_1 , R_2 and R_3 are silyl protecting groups and R_6 is lower alkyl.

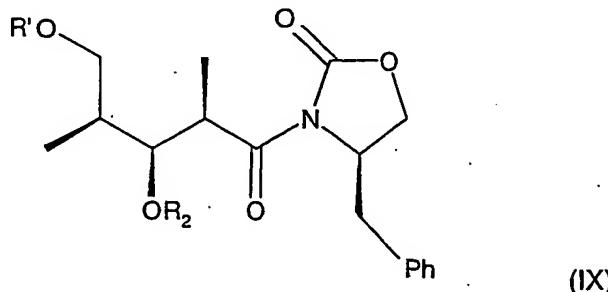
Furthermore, the invention especially relates to an alcohol of formula IV wherein R_1 , R_2 and R_3 are all protecting groups for a hydroxy group which protecting groups can be identical or different and R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy.

Additionally, the present invention relates to a carboxylic ester of formula VII wherein R_3 is hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl.

Furthermore, the invention relates to an oxazolidinone of formula VIII

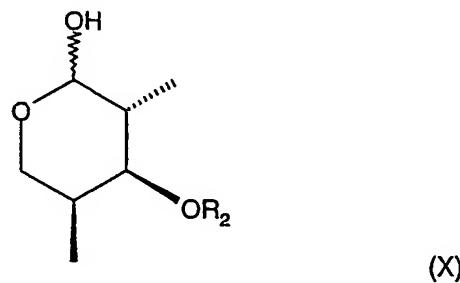


wherein Ph denotes phenyl, and R₁ and R₂ are independently of each other a silyl protecting group, hydrogen or benzyl which is unsubstituted or mono- or disubstituted by lower alkoxy, or R₁ and R₂ together represent methylenediphenyl which phenyl group is mono- or disubstituted by lower alkoxy, and to an oxazolidinone of formula IX

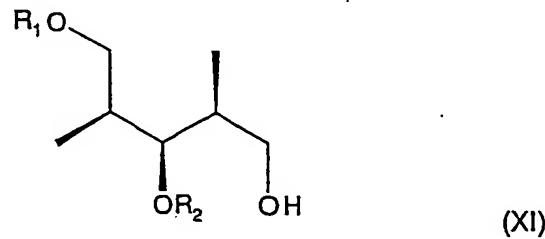


wherein Ph denotes phenyl and R' and R₂ are independently of each other a silyl protecting group, hydrogen or benzyl which is unsubstituted or mono- or disubstituted by lower alkoxy under the proviso that one of both radicals R' and R₂ is a silyl protecting group.

Moreover, the invention relates to a δ -valerolactol of the formula X



wherein R₂ is a protecting group for a hydroxy group and to an alcohol of the formula XI

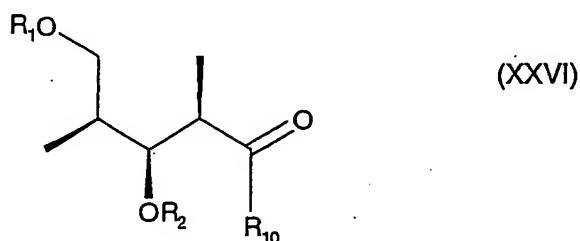


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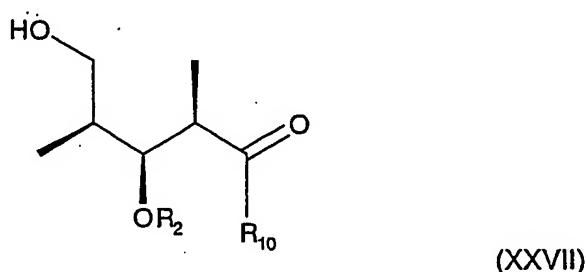
wherein both R_1 and R_2 represent a silyl protecting group.

Additionally, the invention relates to the use of a sulfonate of formula II, of a carboxylic ester of formula III, an alcohol of formula IV or a carboxylic acid of formula VII, all as defined above, in a process for the manufacture of (+)-discodermolide or discodermolide analogues.

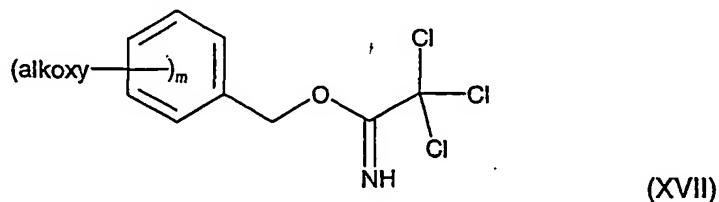
Furthermore, the invention relates to a process for preparing an ether of formula XXVI



wherein R_1 is benzyl which is mono- or disubstituted by alkoxy, R_2 represents a protecting group for a hydroxy group or hydrogen and R_{10} is N-oxazolidinyl which is unsubstituted or substituted by alkyl, benzyl or phenyl; OR_e wherein R_e is alkyl or benzyl, or $N(R_a)_2$ wherein R_a is alkyl or benzyl, in which process a compound of formula XXVII,



in which the radicals R_2 and R_{10} are as defined for the compound of formula XXVI, is reacted with a trichloroacetimidate of formula XVII,



wherein m is 1 or 2 and alkoxy is preferably lower alkoxy, in particular methoxy, in the presence of catalytic amounts of samarium triflate or ytterbium triflate in a suitable solvent, especially dichloromethane, at a temperature between -15 °C and + 15 °C, preferably between -5 °C and +5 °C, in particular at about 0 °C, and afterwards, if desired, the protecting group R_2 is split off.

Within the present disclosure, the general definitions used hereinbefore and hereinafter preferably have the following meaning, if not indicated otherwise:

The prefix "lower" means that the respective moiety preferably has up to and including a maximum of 7 carbon atoms, more preferably up to 4 carbon atoms.

A protecting group for a hydroxy group as defined herein is a protecting group that can be detached under basic or neutral conditions, i.e. in a medium having a pH ≥ 7 , and is especially benzyl which is unsubstituted or mono- or disubstituted by alkoxy, in particular lower alkoxy, preferably methoxy, or, more particular, a silyl protecting group. A silyl protecting group is a group consisting of a silicon atom having a free valence and bearing three groups selected from aryl, alkyl and arylalkyl. A silyl protecting group is in particular a trialkylsilyl- or diaryl-alkylsilyl protecting group, like triethylsilyl, diethyl isopropylsilyl, and, very preferably, *tert*-butyl dimethylsilyl.

Alkyl is preferably lower alkyl which can be linear or branched and is especially ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl or, preferably, methyl or *tert*-butyl.

Alkoxy is preferably lower alkoxy, e.g. ethoxy or *tert*-butoxy, and very preferably methoxy.

Aryl is in particular C_6 - C_{10} aryl, especially phenyl or naphthyl.

Arylalkyl is in particular benzyl.

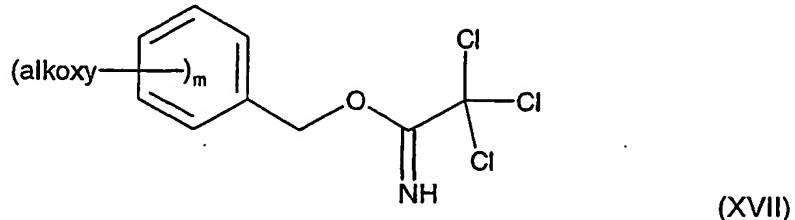
Halogen is preferably fluorine, chlorine, bromine or iodine.

Any reference to other documents or publications within this application means that the respective document or publication is included by reference into the present disclosure.

Substituted alkenes of formula I as defined above are suitable intermediates for the manufacture of (+)-discodermolide and discodermolide analogues.

In particular, a substituted alkene of formula I, wherein all groups R₁, R₂ and R₃ are *tert*-butyl dimethylsilyl, can be selectively transformed into a compound of formula I, wherein R₁ is hydrogen and R₂ and R₃ are both *tert*-butyl dimethylsilyl, by treatment of the compound with trifluoroacetic acid in a mixture of tetrahydrofuran and water. Afterwards, the hydrogen atom in the group R₁ can be replaced by a 4-methoxybenzyl group by further reacting the compound of formula I with a convenient reagent, e.g., 4-methylchloride or -bromide in the presence of Ag₂O in a suitable solvent like dimethylformamide at ambient temperature.

Further suitable reagents and reaction conditions are described by T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, on page 29 and in the references cited there. Very preferably, the hydrogen atom in the group R₁ is replaced by a 4-methoxybenzyl group by reacting a substituted alkene of formula I wherein R₁ is hydrogen with a compound of formula XVII



wherein m is 1 in a suitable solvent like dichloromethane in the presence of a suitable catalyst, e.g., samarium triflate or ytterbium triflate.

The suitability of the resulting substituted alkene of formula I, wherein R₁ is 4-methoxybenzyl, R₂ and R₃ are *tert*-butyl dimethylsilyl and R₄ is 4-methoxyphenyl, for the manufacture of (+)-discodermolide was shown by Amos B. Smith III et al, e.g., in J. Am. Chem. Soc. 2000, 122, 8654-8664, in which publication the transformation of such substituted alkene of formula I (compound "AB" in Scheme 7 on page 8658 and Scheme 9 on page 8659) to (+)-discodermolide is disclosed.

The substituted alkene of formula I, wherein R₁, R₂ and R₃ are independently of each other a protecting group for a hydroxy group or hydrogen and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, is prepared from a sulfonate of formula II, wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different, R₄ has the meaning as defined for the compound of formula I and R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, which sulfonate is reduced, for example, with LiAlH₄, under conditions which are known as such, e.g. by addition of LiAlH₄ to a solution of the compound of formula II in a suitable solvent at a temperature between -100 and -25 °C, e.g. -78 °C. Suitable solvents are, e.g., diethyl ether, diglyme and, in particular, tetrahydrofuran. The reduction can be accomplished, e.g., alternatively with NaBH₄ in a polar aprotic solvent, with LiEt₃BH, with Bu₃SnH-NaI or with NaI and Zn in 1,2-dimethoxyethane.

The reduction of the carboxylic ester of the formula III wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different, R₆ is alkyl or arylalkyl, and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, furnishing an alcohol of the formula IV wherein R₁ to R₄ have the meanings as defined for the compound of formula III, is known as such and can be carried out utilizing reagents like LiBH₄, (isobutyl)₂AlH, lithium triethylborohydride, BH₃-S(methyl)₂ in refluxing tetrahydrofuran, triethoxysilane or sodium in ethanol. Preferably the reaction is carried out using LiAlH₄ in a suitable solvent like tetrahydrofuran.

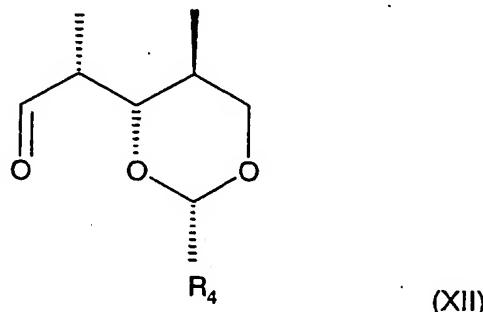
The alcohol of the formula IV wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different, and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, is reacted with a compound of formula V wherein R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, and Hal represent halogen, to a sulfonate of formula II wherein R₁, R₂, R₃ and R₄ have the meanings as defined for the alcohol of formula IV and R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, under conditions known as such. Preferably, the reaction is carried out in the presence of a base, e.g. pyridine, in a suitable inert solvent.

A compound of formula III, wherein R₁ and R₂ are protecting groups for a hydroxy group which protecting groups can be identical or different, R₃ is hydrogen and R₆ is alkyl or arylalkyl, and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, can

also be reacted to a compound of formula I wherein R₁, R₂ and R₄ have the same meaning as in the compound of formula III and R₃ is a protecting group for a hydroxy group in a one-flask synthesis, i.e. without isolating the intermediates described herein.

Preparation of a compound of formula VII

A compound of formula VII, wherein R_3 is hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl is obtained, e.g., by reacting an aldehyde of formula XII

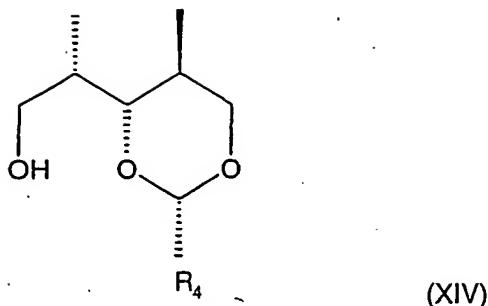


wherein R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy with a compound of formula XIII.



wherein R₆ is alkyl or arylalkyl, in a convenient solvent, in particular, tetrahydrofuran, in the presence of a strong base, preferably lithium diisopropylamide (LDA), and optionally N,N,N',N",N"-hexaméthylphosphotriamide (HMPTA) and a chiral mediator or catalyst, at a temperature between -100 °C and -50 °C, e.g., -78 °C.

An aldehyde of formula XII wherein the radical R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy is prepared by a conventional oxidation reaction, e.g., by a Swern oxidation, of an alcohol of formula XIV,

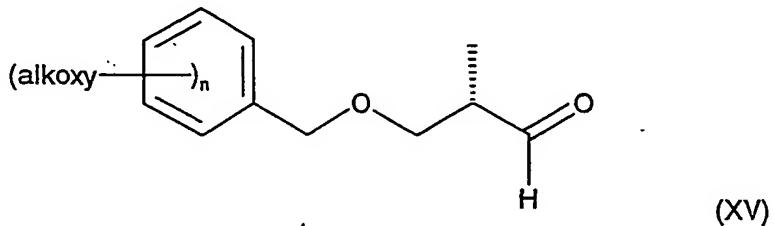


wherein R₄ has the meaning as defined for a compound of formula XII. Preferably, oxalyl chloride in a suitable solvent, e.g., dichloromethane, is mixed with dimethylsulfoxide in the same solvent and the alcohol of formula XIV is then added at a temperature between about -50 °C and -100 °C, e.g., -78 °C. Afterwards, a suitable base, especially diisopropylethylamine, is added at the same temperature.

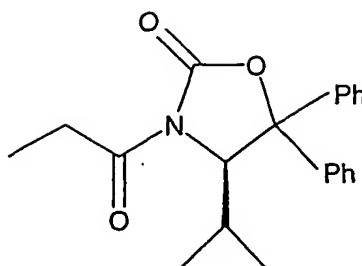
An alcohol of formula XIV wherein R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy is prepared from an acetal of formula VIII wherein R₁ and R₂ together represent methylen substituted by phenyl which phenyl group is mono- or disubstituted by alkoxy by reacting the latter compound with LiAlH₄ in a suitable solvent, especially tetrahydrofuran, at a temperature between about -50 °C and -100 °C, e.g., -78 °C.

An acetal of formula VIII wherein R₁ and R₂ together represent methylen substituted by phenyl which phenyl group is mono- or disubstituted by alkoxy can be obtained by two different synthetic routes:

(a) An aldehyde of formula XV

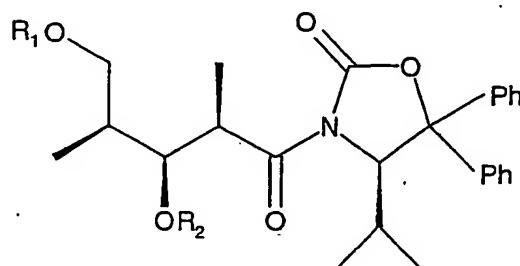


wherein n is 1 or 2, is first reacted with a ketone of formula XVI



(XVI)

wherein Ph denotes phenyl in a suitable solvent, e.g. dichloromethane in the presence of a more than equimolar amount of dibutylboron triflate and a base, preferably, diisopropylethylamine, at a temperature between -15°C and $+15^{\circ}\text{C}$, e.g. 0°C , to furnish an oxazolidinone of formula VIII,



(VIII)

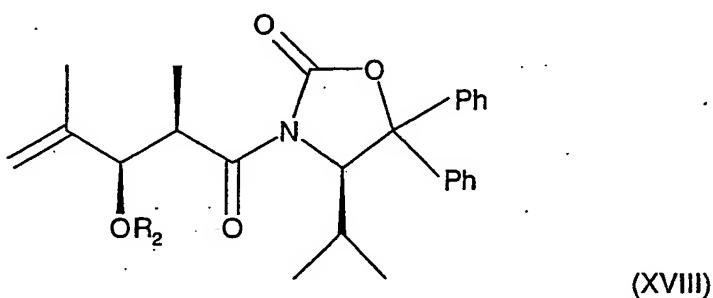
wherein R_1 is benzyl which is mono- or disubstituted by alkoxy, and R_2 is hydrogen.

Such oxazolidinone of formula VIII is further transformed into a corresponding compound of formula VIII wherein R_2 is a protecting group for a hydroxy group which protecting group is not detached by hydrogenolysis, e.g., *tert*-butyl-dimethylsilyl, by reaction with a reagent capable to introduce such protecting group, e.g., by reaction with *tert*-butyl-dimethylsilyl-triflate in a suitable solvent like toluene, chloroform or dichloromethane in the presence of a base, e.g. 2,6-lutidine.

Hydrogenolysis of the obtained silyl-protected compound of formula VIII, e.g., by reaction of such compound with hydrogen in the presence of a catalyst like palladium on charcoal using an alcohol as solvent, provides a compound of formula VIII, wherein R_1 is hydrogen and R_2 is a protecting group for a hydroxy group as defined before.

In an alternative embodiment of the invention a compound of formula VIII, wherein R₁ is hydrogen and R₂ is a protecting group for a hydroxy group is provided by the following route.

A compound of formula XVI as defined above is first reacted with methacrolein in a suitable solvent, e.g. dichloromethane in the presence of a more than equimolar amount of dibutylboryl triflate and a base, preferably, diisopropylethylamine; at a temperature between -15 °C and -90 °C, preferably about -75 to -80 °C, to furnish an oxazolidinone of formula XVIII,

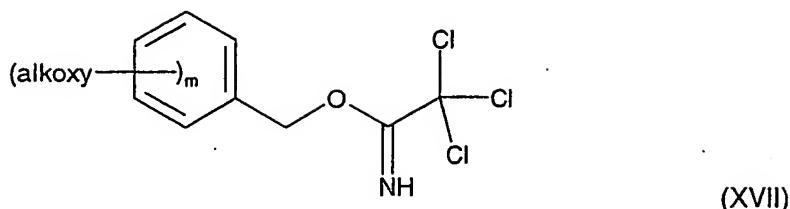


wherein Ph denotes phenyl and R₂ is hydrogen.

Said oxazolidinone of formula XVIII is then further transformed into a corresponding compound of formula XVIII wherein R₂ is a protecting group for a hydroxy group, e.g., *tert*-butyl-dimethylsilyl, by reaction with a reagent capable to introduce such protecting group, e.g., by reaction with *tert*-butyl-dimethylsilyl-triflate in a suitable solvent like toluene, chloroform or dichloromethane in the presence of a base, e.g. 2,6-lutidine.

Finally, the obtained oxazolidinone of formula XVIII wherein R₂ is a protecting group for a hydroxy group is reacted with the *yl* borane, or, preferably, 9-BBN (9-borabicyclo[3.3.1]-nonane) in a suitable solvent, e.g. tetrahydrofuran, at a temperature between -5 °C and +35 °C in order to furnish the compound of formula VIII, wherein R₁ is hydrogen and R₂ is a protecting group for a hydroxy group.

The compound of formula VIII, wherein R₁ is hydrogen and R₂ is a protecting group for a hydroxy group is then contacted with a trichloroacetimidate of formula XVII,



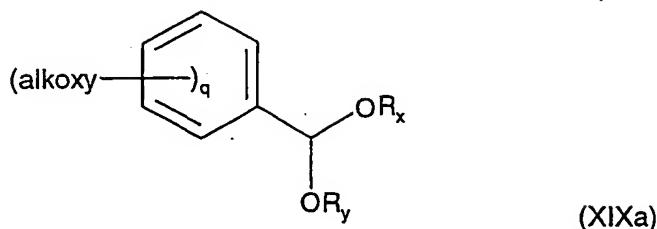
wherein m is 1, 2 or 3, in a suitable solvent like dichloromethane in the presence of a suitable catalyst, e.g., samarium triflate or ytterbium triflate, in order to furnish a compound of formula VIII, wherein R₁ is benzyl which is mono- or disubstituted by alkoxy and R₂ is a protecting group for a hydroxy group which protecting group is not detached by hydrogenolysis.

Such compound of formula VIII is then further reacted with a reagent capable of detaching the protecting group R₂ under conditions leaving the group R₁ unchanged, which conditions are known as such. For example, if R₂ is *tert*-butyl-dimethylsilyl, the reagent capable of detaching such group can be aqueous hydrogenfluoride to be combined with the compound of formula VII in acetonitrile or another suitable lower alkyl cyanide. The reaction provides a compound of formula VII wherein R₁ is benzyl which is mono- or disubstituted by alkoxy and R₂ is hydrogen.

The desired acetal of formula VIII wherein R₁ and R₂ together represent methyldien substituted by phenyl which phenyl group is mono- or disubstituted by alkoxy is obtained by treating such compound of formula VII wherein R₁ is benzyl which is mono- or disubstituted by alkoxy and R₂ is hydrogen with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) which reaction can be carried out in a suitable solvent like dichloromethane at a temperature between -10 °C and +10 °C, preferably at about 0 °C.

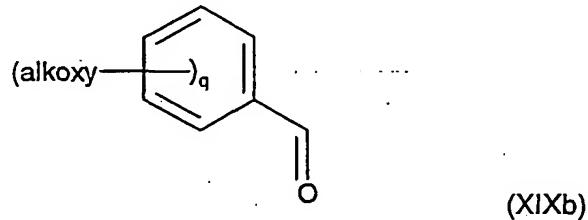
(b) The oxazolidinone of formula XVIII, wherein Ph denotes phenyl and R₂ is hydrogen, obtained as described above, can also be reacted with theyl borane, or, preferably, 9-BBN (9-borabicyclo[3.3.1]nonane) in a suitable solvent, e.g. tetrahydrofuran, at a temperature between -5 °C and +35 °C without prior protection of the hydroxy group present in the compound. The reaction product is a compound of formula VIII wherein R₁ and R₂ are both hydrogen. Such product can be further reacted in a suitable solvent, like dichloromethane, at a temperature, e.g., between 15 °C and 30 °C in the presence of a suitable acid like toluene

sulphonic acid, camphor sulfonic acid or, preferably, Amberlyst 15 with a compound of formula XIXa



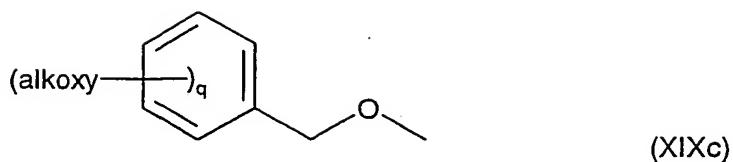
wherein q is 0, 1 or 2, and R_x and R_y are lower alkyl furnishing the desired acetal of formula VIII wherein R₁ and R₂ together represent methylenediphenyl which is mono- or disubstituted by alkoxy.

Alternatively, a compound of formula VIII wherein R₁ and R₂ are both hydrogen can also be transferred into an acetal of formula VIII wherein R₁ and R₂ together represent methylenediphenyl which is mono- or disubstituted by alkoxy by reaction with a compound of formula XIXb



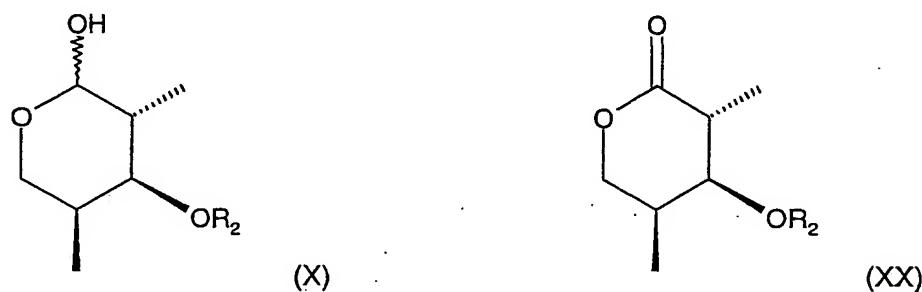
wherein q is 0, 1 or 2, in a suitable solvent, like dichloromethane or benzene, under reaction conditions known as such, especially at the reflux temperature of the solvent optionally in the presence of a reagent that reacts with the water that is obtained in the course of the reaction, like dicyclohexyl carbodiimide.

A further alternative for obtaining an acetal of formula VIII wherein R₁ and R₂ together represent methylenediphenyl which is mono- or disubstituted by alkoxy starting from a compound of formula VIII wherein R₁ and R₂ are both hydrogen constitutes the reaction of the latter compound with a compound of formula XIXc

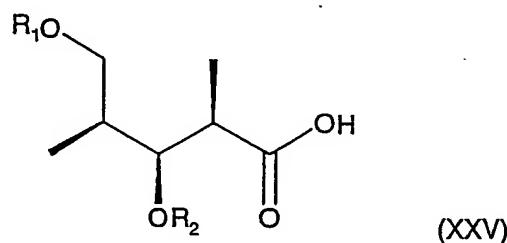


wherein q is 0, 1 or 2 and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a suitable solvent, e.g. dichloromethane, under reaction conditions known as such.

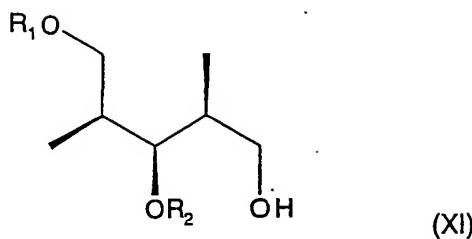
The δ -valerolactol of the formula X and the δ -valerolacton of the formula XX



wherein in both cases R_2 is a protecting group for a hydroxy group are suitable starting materials for the synthesis of the compounds of formula VI and VII. For example, the compound of formula (XX) wherein R_2 is a protecting group for a hydroxy group can be reacted with LiOH and a reagent capable of introducing a protecting group for a hydroxy group R_2 in a suitable solvent to provide a compound of formula XXV



wherein R₁ and R₂ are independently of each other a protecting group for a hydroxy group. Such compound can then be reduced with reagents known as such, e.g. NaBH₄ together with AlCl₃ in diglyme, BH₃ in tetrahydrofuran, LiAlH(O-methyl)₃ in tetrahydrofuran, AlH₃ in diethylether, LiAlH₄ in diethylether or diisobutyl aluminium hydride in tetrahydrofuran, in all cases under conditions known such, to furnish a compound of formula XI



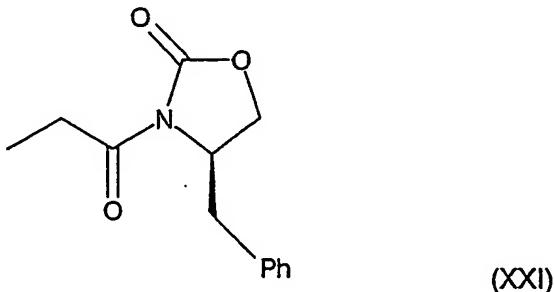
wherein R_1 and R_2 have the meanings as defined for the compound of formula XXV.

Said lactol of formula X is obtained by reacting said lacton of formula XX with DIBAH (diisobutylaluminium hydride) in a suitable solvent, like tetrahydrofuran, at a temperature between about -85 to -70 $^{\circ}\text{C}$.

The lacton of formula XX wherein R_2 is a protecting group for a hydroxy group is the product of the reaction of a compound of formula VIII wherein R_1 is hydrogen and R_2 is a protecting group for a hydroxy group with a catalytic amount of a potassium alcoholate, e.g. potassium *tert*-butanolate, in a suitable solvent, e.g. tetrahydrofuran, at a temperature between about -10 $^{\circ}\text{C}$ and $+10$ $^{\circ}\text{C}$, e.g. 0 $^{\circ}\text{C}$.

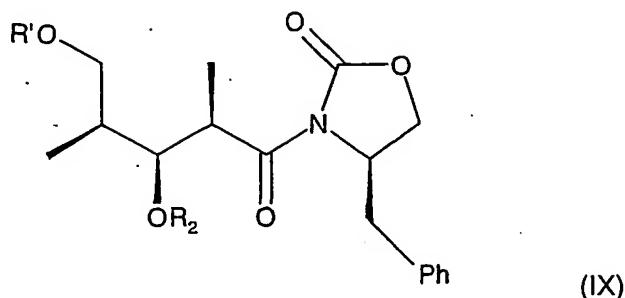
Alternatively, the lacton of formula XX wherein R_2 is a protecting group for a hydroxy group can be prepared by the following synthetic route:

An aldehyde of formula XV wherein n is 1 or 2, is first reacted with a ketone of formula XXI



wherein Ph denotes phenyl, in a suitable solvent, e.g. dichloromethane in the presence of a more than equimolar amount of dibutylboryltriflate and a base, preferably, diisopropyl-

ethylamine, at a temperature between -15°C and $+15^{\circ}\text{C}$, e.g. 0°C , to furnish an oxazolidinone of formula IX,



wherein Ph denotes phenyl and R' is benzyl which is unsubstituted or mono- or disubstituted by alkoxy and R₂ is hydrogen.

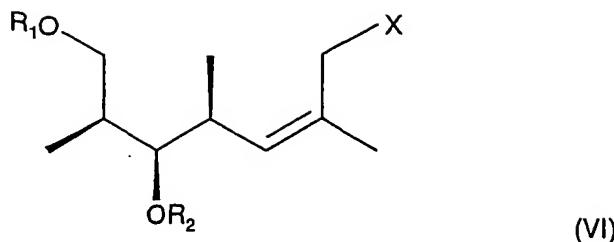
Such oxazolidinone of formula IX is then further transformed into a corresponding compound of formula IX wherein R₂ is a protecting group for a hydroxy group which protecting group is not detached by hydrogenolysis, e.g., *tert*-butyl-dimethylsilyl, by reaction with a reagent capable to introduce such protecting group, e.g., by reaction with *tert*-butyl-dimethylsilyl-triflate in a suitable solvent like toluene, chloroform or dichloromethane in the presence of a base, e.g. 2,6-lutidine.

Hydrogenolysis of the obtained protected compound of formula IX, e.g., by reaction of such compound with hydrogen in the presence of a catalyst like palladium on charcoal using an alcohol as solvent, provides a compound of formula IX, wherein R₁ is hydrogen and R₂ is a protecting group for a hydroxy group as defined before.

Such compound of formula IX, wherein R₁ is hydrogen and R₂ is a protecting group for a hydroxy group which protecting group is not detached by hydrogenolysis provides the desired lacton XX by reaction with H₂O₂ in a mixture of a suitable solvent, e.g. tetrahydrofuran, with water in the presence of LiOH at a temperature between -15°C and $+15^{\circ}\text{C}$, e.g. 0°C .

Preparation of the allyl halide of formula VI

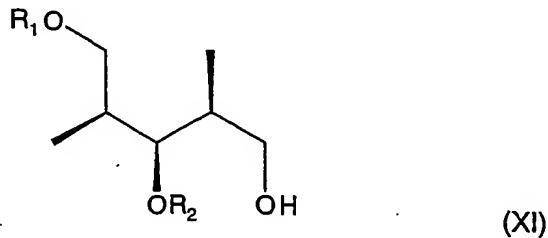
- 20 -



wherein *R*₁ and *R*₂ are protecting groups for a hydroxy group which protecting groups can be identical or different and *X* is halogen is obtained by the following reaction steps:

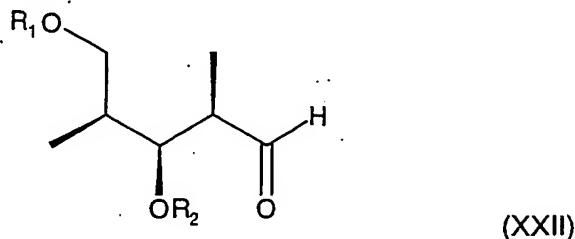
The oxazolidinone of formula VIII, wherein Ph denotes phenyl and wherein *R*₁ and *R*₂ are both hydrogen, obtained as described above, is transformed into a corresponding compound of formula VIII wherein *R*₁ and *R*₂ are both protecting groups for a hydroxy group which protecting groups are not detachable under the reaction conditions of the following reaction steps providing the desired compound of formula VI, preferably a silyl protecting group for a hydroxy group, e.g., *tert*-butyl-dimethylsilyl, by reaction with a reagent capable to introduce such protecting groups, e.g., by reaction with *tert*-butyl-dimethylsilyl-triflate in a suitable solvent like toluene, chloroform or dichloromethane in the presence of a base, e.g. 2,6-lutidine.

The latter compound of formula VIII is then reacted with a suitable reduction reagent, preferably LiBH₄, in a suitable solvent, e.g. a mixture of tetrahydrofuran and water, at a temperature between about -5 °C and + 30 °C to provide an alcohol of the formula XI

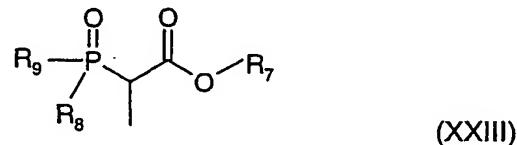


wherein both *R*₁ and *R*₂ represent a protecting group for a hydroxy group which protecting group is not detachable under the reaction conditions of the following reaction steps providing the desired compound of formula VI, preferably a silyl protecting group.

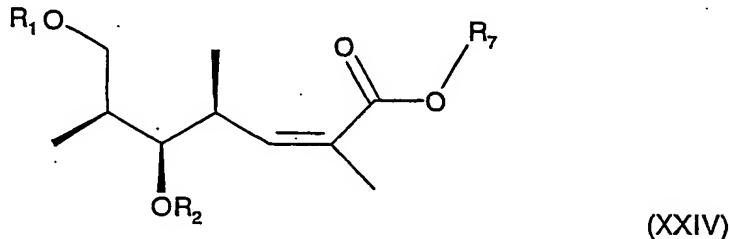
Such alcohol of formula XI is then oxidized by a suitable reagent, preferably via Swern oxidation, to the corresponding aldehyde of formula XXII



wherein R₁ and R₂ are as defined above for a compound of formula XI. Wittig olefination with a phosphonate of formula XXIII



wherein R₇ is alkyl or arylalkyl and R₈ and R₉ are independently of each other alkyl which is unsubstituted or substituted by halogen, preferably fluorine, provides an α,β -unsaturated carboxylic acid ester of formula XXIV



wherein R₁ and R₂ are as defined above for a compound of formula XI and R₇ is alkyl or arylalkyl. The reaction is preferably accomplished in tetrahydrofuran in the presence of the base potassium hexamethyldisilazane and 18-crown-6.

Said compound of formula XXIV is further reacted with DIBAH or another reagent, especially a reagent disclosed herein, capable of transforming a carboxylic ester into an alcohol, in a suitable solvent, for example, in the case of DIBAH in dichloromethane, to furnish an allylic

alcohol of formula VI wherein R₁ and R₂ are protecting groups for a hydroxy group which protecting groups can be identical or different and X is hydroxy.

Finally, the allylic alcohol of formula VI is transformed into the desired allylic halide of formula VI, preferably an allylic iodide by reaction with iodine in the presence of triphenylphosphine and imidazole in a suitable solvent, e.g., a mixture of diethylether and a lower alkyl nitrile.

The skilled person will understand that the reaction conditions given above can be replaced by analogous reaction conditions that are in principle known in the art. Furthermore, a person skilled in the art will be aware of suitable protecting groups of hydroxy that can replace the protecting groups used in the specific Examples below and how to attach such groups to free hydroxy groups present in the compounds described hereinbefore and hereinafter, especially in a compound of formula I, IV, VIII or IX, and how to detach such groups, if desired. In addition, the skilled person will be able to select the appropriate specific reaction conditions for the reaction steps given hereinbelow and hereinafter where reactions are described generally herein. All those reaction conditions are included in the scope of the present invention.

The protection of hydroxy groups by protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

The following examples are for purposes of illustration only and are not intended to limit in any way the scope of the instant invention. Starting materials can be purchased or prepared by the methods mentioned hereinafter.

Abbreviations:

aqu.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
brine	saturated sodium chloride solution
bu	butyl
DIBAH	diisobutylaluminium hydride
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethyl sulfoxide
Et	ethyl
EtOAc	ethyl acetate
FC	flash-chromatography
h	hour(s)
HMPA	N,N,N',N",N"-hexamethylphosphotriamide
HRMS	high resolution mass spectrometry
K	Kelvin
KHMDS	potassium hexamethyldisilazane
min	minute(s)
m.p.	melting point
Me	methyl
MS	mass spectrometry
MS (EI)	electrospray ionisation mass spectrum
Ph	phenyl
PTLC	preparative thin layer chromatography
RT	room temperature
sat.	saturated
TBDMS	<i>tert</i> -butyl-dimethylsilyl
TBME	<i>tert</i> -butyl methyl ether
TBSOTf	<i>tert</i> -butyl-dimethylsilyl-trifluoromethanesulfonate
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran

Abbreviations for the NMR spectra data

b	broad
d	doublet

J	coupling constant
m	multiplet
q	quartet
s	singlet
t	triplet
ppm	parts per million

Example 1: (4*R*)-4-Benzyl-(*N*)-[(2*R*, 3*S*, 4*S*)-5-(4-methoxybenzyloxy)-2,4-dimethyl-3-(*tert*-butyl-dimethylsilyloxy)-valeryl]-oxazolidin-2-one

The alcohol from stage 1.1 (1.36 g, 3.1 mmol) is dissolved in 10 mL of CH₂Cl₂ under an atmosphere of argon and cooled to 0 °C. 2,6-Lutidine (0.49 mL, 4.0 mmol, 1.3 eq.) is added followed by dropwise addition of TBSOTf (0.78 mL, 3.4 mmol, 1.1 eq.). The reaction mixture is stirred for 30 min, poured onto ice water and extracted with hexane. The organic layer is washed with 1N HCl, sat. aqu. NaHCO₃ and sat. aqu. NaCl, then dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a colorless oil.

Stage 1.1: A solution of (*R*)-4-benzyl-(*N*)-propionyloxazolidin-2-one (Aldrich, 336 mg, 1.44 mmol) in 3.0 mL dichloromethane is treated with a 1.0 M solution (1.6 mL, 1.6 mmol) of Bu₂BOTf at 0 °C under an atmosphere of argon. To the resulting brown-red mixture 0.30 mL (1.7 mmol) of diisopropylethylamine is added to give a colorless, clear solution, which is stirred a 0 °C for 1 h. Then a solution of (*S*)-3-(4-methoxybenzyloxy)-2-methyl-propion-aldehyde (Aldrich, 300 mg, 1.44 mmol) dissolved in 1.5 mL of CH₂Cl₂ is added slowly at -78 °C. The reaction mixture is stirred at this temperature for 60 min and at 0 °C for 45 min. Phosphate buffer pH 7.0 is added followed by extraction (3 times) with TBME. The combined organic layers are washed with sat. aqu. NaCl solution, dried over MgSO₄ and concentrated *in vacuo*. The residue is redisolved in 5 mL of methanol and treated with 2 mL of aqu. H₂O₂ (30%) at 0 °C. After stirring for 1 hour the volatiles are removed *in vacuo* and the aqueous phase is extracted with TBME (3 times). The combined organic layers are washed with sat. NaHCO₃ and brine, dried over MgSO₄, and concentrated *in vacuo*. After chromatographic purification (SiO₂, heptane/ ethylacetate 2:1) the desired alcohol is obtained as a colorless oil.

Example 2: (4*R*)-4-Benzyl-(*N*)-[(2*R*, 3*S*, 4*S*)-5-hydroxy-2,4-dimethyl-3-(*tert*-butyl-dimethylsilyloxy)-valeryl]-oxazolidin-2-one

A solution of 132 mg (0.24 mmol) of the TBDMS ether from Example 1 in 3.0 mL of methanol is hydrogenated in the presence of a catalytic amount of Pd/C under 1 bar of hydrogen atmosphere for 6 h at 23 °C. After filtration of the reaction mixture through a pad of cellflock which is washed 3 times with ethylacetate, concentration *in vacuo* and FC (SiO₂, hexanes/EtOAc 1:1), the title compound is obtained as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz, 300K) δ 7.32-7.05 (m, 5H), 4.62-4.52 (m, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 4.12-4.0 (m, 2H), 3.50 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.42 (dd, *J* = 12.0, 6.8 Hz, 1H), 3.19 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.70 (dd, *J* = 13.5, 9.0 Hz, 1H), 1.9-1.85 (m, 1H), 1.65-1.45 (br m, 1H), 1.20 (d, *J* = 8.3 Hz, 3H), 0.92 (d, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H). MS (EI) *m/z* 458 (100, [M + Na]⁺).

Example 3: (1*RS*, 2*R*, 3*S*, 4*S*)-5-Hydroxy-2,4-dimethyl-3-*tert*-butyl-dimethylsilyloxy-δ-valerolactol

The lactone of stage 3.1 (1.00g, 3.87 mmol) is dissolved in 40 mL of toluene and 3.10 mL (4.65 mmol) of DIBAH (1.5 M in toluene) is added over 10 min at -78 °C. After 30 min at -78 °C, the reaction mixture is quenched by addition of 2 mL of MeOH. The resulting mixture is poured on aqu. sat. NH₄Cl and the two layers are separated. The aqu. layer is extracted (3 times) with EtOAc. The combined organic phases are washed successively with 10% aqu. H₂SO₄, sat. aqu. NaHCO₃ and sat. aqu. NaCl, dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz, 300K, mixture of anomers, ratio = 4.2:1.0) major anomer: δ 4.68 (br s, 1H); 3.72 (dd, *J* = 11.2, 0.8 Hz, 1H); 3.62 (br m, 1H), 3.32 (dd, *J* = 11.2, 5.6 Hz, 1H); 2.02-1.85 (two m, 2H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.75 (d, *J* = 7.5 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H); minor anomer: δ 5.00 (d, *J* = 1.9 Hz, 1H), 3.80-3.67 (m, 1H, obscured by one signal from the major anomer), 3.43 (dd, *J* = 11.3, 7.1 Hz, 1H), 2.05-1.80 (two m, 2H), 0.90 (d, *J* = 7.3 Hz, 3H), 0.84 (s, 9H), 0.82 (d, *J* = 7.5 Hz, 3H), 0.00 (s, 3H), ?0.3 (s, 3H); MS (EI) *m/z* 244 (7, [M - O]⁺), 204 (55, [M - C(CH₃)₃]⁺), 145 (100, [M - Si(CH₃)₂(CH₃)₃]⁺).

Stage 3.1: A solution of the alcohol from Example 2 (43 mg, 0.1 mmol) in 1.5 mL of THF/H₂O (3:1) is treated with 40 μ l (0.4 mmol, 4.0 eq.) of H₂O₂ (30%) followed by 8 mg (0.2

mmol, 2.0 eq.) of LiOH monohydrate at 0 °C. After stirring for 40 min, 0.3mL of a 1.5 M aqu. solution of Na₂SO₃ is added. The reaction is quenched with sat. aqu. NaHCO₃ and extracted with TBME. The ether layer is washed with sat. aqu. NaHCO₃ solution twice. The combined aqu. extracts are acidified (pH 3) with 1 N HCl and extracted with ethylacetate (3 times). The organic layers are combined, dried over MgSO₄ and concentrated *in vacuo* to give the desired lactone as a colorless crude oil containing some oxazolidinone as the major impurity. ¹H-NMR DMSO-d⁶, 400 MHz, 300K) δ 4.20 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.07 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.83 (dd, *J* = 5.3, 2.8 Hz, 1H), 2.47 (qd, *J* = 7.8, 5.3 Hz, 1H), 2.28-2.15 (m, 1H), 1.20 (d, *J* = 7.8 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). MS (EI) *m/z* 539 (30, [M + 2 Na]⁺), 322 (55, [M + CH₃CN]⁺).

Example 4: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-5-hydroxy-2,4-dimethyl-3-(*tert*-butyl-dimethylsilyloxy)-valeryl]-oxazolidin-2-one

To a solution of 7.67 g (14.7 mmol) of the TBDMS ether of stage 4.2 in 60 mL of THF at 0 °C under an atmosphere of argon is added 3.59 g (29.4 mmol) of 9-BBN in 50 mL of THF. After 15 min at 0 °C the reaction mixture is warmed to ambient temperature with stirring for 5 h. The mixture is recooled to 0 °C and quenched with 19.4 mL each of 1:1 (v/v) EtOH/ THF, aqu. pH 7 phosphate buffer, and 35% aqu. hydrogen peroxide. After 30 min, the solution is again warmed to ambient temperature and stirred for 15 h. Heptane (150 mL) and 20% aqu. NaHSO₃ (120 mL) are added and the aqu. layers are extracted with heptane (2 x 100 mL). The combined organic layers are washed with sat. aqu. NaCl (1 x 100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by FC (SiO₂, hexane/ACOEt 4:1) gives the title compound as a colorless oil which crystallizes upon conservation at 4 °C. ¹H-NMR (CDCl₃, 300 MHz, 300K) δ 7.55-7.15 (4 m, 10H), 5.27 (d, *J* = 3.5 Hz, 1H), 3.95 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.76 (qd, *J* = 9.4, 6.9 Hz, 1H), 2.91 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.49 (dd, *J* = 12.0, 7.5 Hz, 1H), 1.79 (heptuplet, *J* = 6.8, 3.5 Hz, 1H), 1.72-1.65 (br s, 1H), 1.33-1.18 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.83, (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.58 (d, *J* = 7.1 Hz, 3H), 0.00 (s, 6H).

The title compound is converted to the lactone of stage 3.1 using the following procedure:

The title compound (2.08g, 3.85 mmol) is dissolved in 40 mL of THF and a solution of *t*-BuOK (1.5 M in THF, 77 μL, 77 μMol) is added at 0 °C under an atmosphere of argon. The

clear, colorless solution is allowed to stir for 1h and to warm up to 23 °C. A white precipitate is formed. The reaction mixture is diluted with 50 mL of hexane and is filtered. The residue is washed with aqu. sat. NaCl. The filtrate is collected and the two layers separated. The organic layer is dried over MgSO₄ and partially concentrated *in vacuo*. A white precipitate is formed during the concentration. The mixture is filtered and the residue is washed with 5 mL of hexane. The filtrate is collected and concentrated *in vacuo* to give the pure lactone of stage 3.1 as a colorless oil which solidified upon conservation at 4 °C providing a solid having a m.p. of 53-54 °C.

Stage 4.1: A solution of 14.9 mL (87 mmol, 1.45 eq.) of diisoproylethylamine in 30 mL of CH₂Cl₂ under an atmosphere of argon is treated sequentially at -5 °C over 10 min with a 1.0 M solution (78 mL, 78 mmol, 1.3 eq.) of Bu₂BOTf in CH₂Cl₂ and at -78 °C over 15 min with a solution of (*R*)-4-isopropyl-5,5-diphenylpropionyloxazolidin-2-one (20.2 g, 60 mmol; prepared according to T. Hintermann, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2093) in 60 mL of CH₂Cl₂ to give a clear orange solution. After 10 min at -78 °C, the solution is warmed to 0 °C with stirring for 1 h, after which it is recooled to -78 °C again. A solution of methacrolein (14.8 mL, 180 mmol, 3 eq.) dissolved in 20 mL of CH₂Cl₂ is then added slowly over a period of 30 min. After 30 further min stirring, the reaction mixture is warmed to 0 °C with stirring for 1h. Phosphate buffer pH 7.0 (60 mL), MeOH (180 mL) and MeOH/35% H₂O₂ (2:1 v/v, 180 mL) are added sequentially at 0 °C. After stirring for 3 h at ambient temperature, the mixture is recooled to 0 °C and treated with 40% aqu. NaHSO₃ (80 mL). The volatiles are removed *in vacuo* and the aqu. phase is extracted with toluene (3 x 200 mL). The combined organic layers are washed with 1N HCl (60 mL), sat. aqu. NaHCO₃ (60 mL) and sat. aqu. NaCl (60 mL) solutions, dried over MgSO₄, filtered, and concentrated *in vacuo* to give 28.6 g of the desired alcohol as slightly yellowish crude solid residue, a sample of which is purified by FC (SiO₂, hexane/ AcOEt 3:1) to afford the pure alcohol as white crystals with a m.p. of 99.5-100.0 °C.

Stage 4.2: The crude alcohol of stage 4.1 (13.9 g) is dissolved in 50 mL of CH₂Cl₂ under argon and cooled to 0 °C. 2,6-Lutidine (4.9 mL, 42 mmol) is added followed by dropwise addition over 10 min of TBSOTf (7.1 mL, 31 mmol). The reaction mixture is stirred for 30 min at 0 °C, after which 100 mL of hexane and 45 mL of 1N HCl are added sequentially. The aqu. layer is extracted (2 times) with hexane. The combined organic layers are washed with 1N HCl (2 times), sat. aqu. NaHCO₃ and sat. aqu. NaCl, then dried over MgSO₄ and

concentrated *in vacuo* to give 17.7 g of the crude product as yellow crystals. After recrystallization from 20 mL of hexane with addition of seed crystals, the desired TBDMS ether is obtained as slightly yellowish crystals with a m.p. of 116 °C.

Example 5: (4*R*)-4-isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-5-hydroxy-2,4-dimethyl-3-(*tert*-butyl-dimethylsilyloxy)-valeryl]-oxazolidin-2-one

A solution of 110 mg (0.17 mmol) of the TBDMS ether of stage 5.2 in 3.0 mL MeOH is hydrogenated in the presence of a catalytic amount of Pd/C under 1 bar of hydrogen atmosphere for 5 h at 23 °C. After filtration of the reaction mixture through a pad of cellflock which is washed 3 times with MeOH, concentration *in vacuo* and FC (SiO₂, hexane/EtOAc 5:1) the title compound is obtained as a white solid (physical data see Example 4).

Stage 5.1: A solution of (*R*)-4-isopropyl-5,5-diphenylpropionyloxazolidin-2-one (see stage 4.1; 1.00g, 2.96 mmol) in 7.5 mL of dichloromethane is treated with a 1.0 M solution (3.55 mL, 3.55 mmol) of Bu₂BOTf at 0 °C under an atmosphere of argon. To the resulting brown-red mixture 0.66 mL (3.85 mmol) of diisopropylethylamine is added to give a colorless, clear solution, which is stirred a 0 °C for 1 h. Then a solution of (*S*)-3-(4-methoxybenzyl)-2-methyl-propionaldehyde (Aldrich, 616 mg, 2.96 mmol) dissolved in 1.0 ml of CH₂Cl₂ is added slowly at -78 °C. The reaction mixture is stirred at this temperature for 60 min and at 0 °C for 60 min. Phosphate buffer pH 7.0 (3.0 mL), MeOH (8.9 mL) and MeOH/30% H₂O₂ (2:1 v/v, 8.9 mL) are added sequentially at 0 °C. After stirring for 1 h at RT, the volatiles are removed *in vacuo* and the aqu. phase is extracted with TBME (3 times). The combined organic layers are washed with 1N HCl, sat. aqu. NaHCO₃ and sat. aqu. NaCl solutions, dried over MgSO₄ and concentrated *in vacuo*. After chromatographic purification (SiO₂, heptane/EtOAc 4:1) the desired alcohol is obtained as a colorless oil.

Stage 5.2: The alcohol from stage 5.1 (96 mg, 0.18 mmol) is dissolved in 5 mL of CH₂Cl₂ under argon and cooled to 0 °C. 2,6-Lutidine (31 µL, 0.27 mmol) is added followed by dropwise addition of TBSOTf (50 µL, 0.22 mmol). The reaction mixture is stirred for 45 min at 0 °C, poured onto ice water and extracted with TBME (3 times). The combined organic layers are washed with 1N HCl, sat. aqu. NaHCO₃ and sat. aqu. NaCl, then dried over MgSO₄ and concentrated *in vacuo* to give the desired product as a colorless oil.

Example 6: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-3,5-dihydroxy-2,4-dimethyl-valeryl]-oxazolidin-2-one

To a solution of 10.2 g (25.0 mmol) of the allylic alcohol from stage 4.1 in 100 mL of THF at 0 °C under an atmosphere of argon, a solution of 9-BBN (7.56 g, 62.0 mmol, 2.5 eq.) in 130 mL of THF is added over a period of 30 min. After 10 min at 0 °C the reaction mixture is warmed to ambient temperature with stirring for 6.5 h. The mixture is recooled to -15 °C and quenched with 78 mL each of 1:1 (v/v) EtOH/THF, aqu. pH 7 phosphate buffer, and 35% aqu. hydrogen peroxide. After 30 min, the solution is again warmed to ambient temperature and stirred for 15 h. A 40% aqu. solution of NaHSO₃ (210 g) and heptane (200 mL) are added sequentially and the aqu. layers are extracted with heptane (2 x 150 mL). The combined organic layer is washed with 0.2 N NaOH (2 x 100 mL), sat. aqu. NH₄Cl (1 x 100 mL), and sat. aqu. NaCl (1 x 100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by FC (SiO₂, hexane/AcOEt 1:1) gives 7.38 g of the title compound as a colorless oil which crystallizes upon conservation at 4 °C providing a solid with a m.p. of 103-104 °C.

Example 7: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-3,5-bis(*tert*-butyl-dimethylsilyloxy)-2,4-dimethyl-valeryl]-oxazolidin-2-one

The alcohol of Example 6 (1.10 g, 2.04 mmol) is dissolved in 20 mL of CH₂Cl₂ under an atmosphere of argon and cooled to 0 °C. 2,6-Lutidine (0.28 mL, 2.45 mmol, 1.20 eq.) is added followed by dropwise addition of TBSOTf (0.49 mL, 2.14 mmol, 1.05 eq.). The reaction mixture is stirred for 60 min, poured onto 1 N HCl and extracted with heptane (3 times). The organic layer is washed with sat. aqu. NaHCO₃ and sat. aqu. NaCl, then dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a colorless oil which crystallizes upon conservation at 4 °C providing a solid with a m.p. of 104-105 °C.

Example 8: (2*S*, 3*S*, 4*S*)-3,5-Bis(*tert*-butyl-dimethylsilyloxy)-2,4-dimethyl-pentan-1-ol

A 2.0 M solution of LiBH₄ (6.55 mL, 13.10 mmol) in THF is added to a solution of the bis-TBDMS ether of Example 7 (5.36 g, 8.19 mmol) in 130 mL of diethylether and 234 µL (13.02 mmol) of water at 0 °C over a period of 10 min. The mixture is allowed to warm to ambient temperature over night. The chiral auxiliary forms a white crystalline precipitate. Another 73

μL (4.06 mmol) water and 2.05 mL (4.09 mmol) of a 2 M LiBH₄ solution are added at 23 °C. After additional 6.5 h reaction time further 73 μL (4.06 mmol) water and 2.05 mL (4.09 mmol) of a 2 M LiBH₄ solution are added at 23 °C and the resulting mixture is stirred over night. The reaction is quenched by adding 200 mL of 1 N NaOH followed by the addition of 400 mL ethylacetate. The phases are separated and the aqu. layer is extracted twice with 150 mL ethylacetate. The combined organic phases are washed with brine (250 mL), dried over MgSO₄ and concentrated in vacuo. The residue is suspended in 80 mL heptane, stirred at 0 °C for 1.5 h and filtered. The obtained cake is washed with cold heptane (75 mL) and dried at 50 °C in vacuo to give recycled auxiliary. The combined filtrates are concentrated to provide the crude title compound as a colorless oil.

cis-(4*S*, 5*R*, 6*S*)-5,7-Bis(*tert*-butyl-dimethylsilyloxy)-2,4,6-trimethyl-hept-2-en-1-yl iodid can be obtained from the title compound by the following procedure:

Stage 8.1: A solution of 0.455 mL (5.30 mmol) oxalylichloride in 20 mL CH₂Cl₂ is treated with a solution of 0.75 mL (10.6 mmol) DMSO in 1.0 mL CH₂Cl₂ at -78 °C. After 15 min a solution of the title compound (1.0 g, 2.65 mmol) in 8 mL CH₂Cl₂ is added dropwise over a period of 30 min. Et₃N (2.3 mL, 15.9 mmol) is added over 12 min and the reaction mixture is allowed to warm to room temperature. After additional stirring for 30 min 40 mL TBME and 50 mL of a sat. NH₄Cl solution are added. The aqu. layer is separated and extracted twice with 30 mL TBME. The combined organic layers are washed with 50 mL brine, dried over MgSO₄ and concentrated under reduced pressure. The residual oil is purified by FC (heptane/ethylacetate 100:1.5) to give the desired aldehyde as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz, 300K) δ = 9.67 (s, 1H), 4.19 (dd, *J* = 6.6, 3.2 Hz, 1H), 3.52 (ddd, *J* = 25.7, 10.0, 5.7 Hz, 2H), 2.44-2.47 (m, 1H), 1.78-1.87 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), 0.00 (2s, 6H), -0.05 (s, 3H).

Stage 8.2: A solution of 2-[bis-(2,2,2-trifluoroethyl)]-phosphono propionic acid ethyl ester (0.948g, 2.74 mmol, prepared analog to the procedure described in Synthesis 1986, 16(11) 1285-1295) and 18-crown-6 (2.0 g, 10.0 mmol) in 20 ml THF is treated with 5.5 mL (2.74 mmol) of a 0.5 M solution of KHMDS in toluene at -78 °C. After 5 min a solution of the aldehyde of stage 8.1 (1.029 g, 2.74 mmol) in 8 ml THF is added dropwise over 15 min. The pale yellow reaction mixture is stirred for additional 45 min at 0 °C. Then 20 mL TBME and 20 mL of a sat. NH₄Cl solution is added followed by the addition of 10 mL of water. The

layers are separated and the aqu. phase is extracted with 90 mL TBME. The combined organic layers are washed with brine and concentrated *in vacuo*. The residue is suspended in 10 mL of n-heptane, stirred for 10 min and filtered. The filtrate is concentrated to give the desired *cis*-ethylester.

Stage 8.3: A solution of the ethylester of stage 8.2 (97 mg, 0.21 mmol) in 5 mL of CH_2Cl_2 is treated with a 1.5 M solution in toluene of DIBAH (0.42 mL, 0.63 mmol, 3.0 eq.) at -78 °C under an atmosphere of argon. The reaction mixture is warmed to 0 °C with stirring for 30 min, after which it is quenched by addition of a 10% aqu. solution of H_2SO_4 . The aqu. layer is extracted (3 times) with EtOAc. The combined organic layers are washed with sat. aqu. NaHCO_3 and sat. aqu. NaCl , then dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by FC (SiO_2 , hexane/AcOEt 9:1) provides the desired allylic alcohol as a colorless oil.

Stage 8.4: A solution of the allylic alcohol of stage 8.3 (59 mg, 0.14 mmol) in 4 mL of a mixture of $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$ (1:3 v/v) is treated with PPh_3 (55 mg, 0.21 mmol, 1.5 eq.), imidazole (14 mg, 0.21 mmol, 1.5 eq.), and iodine (53 mg, 0.21 mmol, 1.5 eq.) at 0 °C under an atmosphere of argon. The resulting yellow suspension is stirred for 30 min at 0 °C, after which a sat. aqu. solution of NaHSO_3 is added. The aqu. layer is extracted with TBME (3 times). The combined organic layers are washed with 1N HCl, sat. aqu. NaHCO_3 and sat. aqu. NaCl , then dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by FC (SiO_2 , hexane/AcOEt 20:1) gives the desired allylic iodide as a slightly yellowish oil.

Example 9: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-5-(4-methoxybenzyloxy)-2,4-dimethyl-3-(*tert*-butyl-dimethylsilyloxy)-valeryl]-oxazolidin-2-one

A solution of the alcohol of Example 4 (3.61g, 6.69 mmol) in 55 mL of CH_2Cl_2 is treated with SmOTf_3 (160 mg, 0.27 mmol, 4 mol%) at 23 °C under an atmosphere of argon. The slightly turbid solution is cooled to -20 °C and treated by dropwise addition over a period of 45 min with a solution of 4-methoxybenzyl-2,2,2-trichloroacetimidate (2.27 g, 8.03 mmol, 1.20 eq., prepared according to the method described in *Tetrahedron* 1999, 55, 1607-1630) in 55 mL of CH_2Cl_2 . At the end of the addition, the resulting reaction mixture is stirred at -20 °C for 30 min, after which it is warmed to -10 °C and treated with 50 mL of water. The layers are separated. The organic layer is washed with 0.5 N NaOH (50 mL) and aqu. sat. NaCl (50

mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. After purification by FC (SiO_2 , hexane/AcOEt 5:1), the title compound is obtained as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz, 300K) δ = 7.50-7.22 (m, 12H), 6.83-6.78 (m, 2H), 5.39 (d, J = 3.3 Hz, 1H), 4.00-3.83 (m, 4H), 3.78 (s, 3H), 3.08 (dd, J = 9.4, 6.5 Hz, 1H), 2.72 (dd, J = 9.4, 7.1 Hz, 1H), 1.98 (heptupletd, J = 6.8, 3.3 Hz, 1H), 1.60 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.81 (s, 9H), 0.76 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H), 0.00 (s, 3H), -0.02 (s, 3H).

Example 10: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[(2*R*, 3*S*, 4*S*)-3-hydroxy-5-(4-methoxybenzyl)-2,4-dimethyl-valeryl]-oxazolidin-2-one

A solution of the PMB ether of Example 9 (162 mg, 0.25 mmol) in 5 mL of CH_3CN at 23 °C is treated with 0.5 mL of 48% aqu. HF. After stirring for 24 h, the reaction is quenched with sat. aqu. NaHCO_3 and extracted with TBME (3 times). The combined organic layers are washed with sat. aqu. NaHCO_3 and sat. aqu. NaCl , dried over MgSO_4 , filtered, and concentrated *in vacuo*. After purification by FC (SiO_2 , heptane/AcOEt 3:1), the title compound is obtained as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz, 300K) δ 7.45-7.05 (m, 12H), 6.85-6.75 (m, 2H), 5.26 (d, J = 3.5 Hz, 1H), 4.24 (d, J = 11.5 Hz, 1H), 4.15 (d, J = 11.5 Hz, 1H), 3.73 (s, 3H), 3.70 (qd, J = 6.9, 5.4 Hz, 1H), 3.32 (m, 1H), 3.15 (d, J = 5.0 Hz, 1H), 3.05 (dd, J = 9.3, 4.4 Hz, 1H), 2.97 (dd, J = 9.3, 5.1 Hz, 1H), 1.90 (heptupletd, J = 6.8, 3.5 Hz, 1H), 1.58-1.40 (m, 1H), 1.22 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H); HRMS (ESI) m/z 568.2671 ($[\text{M} + \text{Na}]^+$; calcd. for $\text{C}_{33}\text{H}_{39}\text{NO}_6$: 568.2671).

Example 11: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[2-((1*S*, 3*R*, 6*S*)-3-(4-methoxyphenyl)-6-methyl-2,4-dioxacyclohex-1-yl)-(2*R*)-propionyl]-oxazolidin-2-one

To a solution of the alcohol of Example 10 (54 mg, 0.10 mmol) in 1.0 mL of CH_2Cl_2 at 0 °C under an atmosphere of argon, 4 Å molecular sieve (55 mg) and DDQ (30 mg, 0.13 mmol, 1.3 eq.) are added sequentially in one portion. The resulting deep green reaction mixture is stirred at 0 °C for 15 h. A precipitate is formed. After removal of the precipitate by filtration, concentration *in vacuo* and PTLC (SiO_2 , 10x20 cm plate, heptane/AcOEt 2:1), the title compound is obtained as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz, 300K) δ 7.40-7.15 (two m, 8H), 7.22 (d, J = 8.7 Hz, 2H), 7.07-6.94 (m, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.22 (d, J = 3.4 Hz, 1H), 4.49 (s, 1H), 4.00 (qd, J = 6.9, 3.4 Hz, 1H), 3.85 (dd, J = 11.2, 4.6 Hz, 1H), 3.75 (s,

3H), 3.13 (t, J = 11.2 Hz, 1H), 3.11 (dd, J = 9.7, 3.4 Hz, 1H), 1.93 (heptupletd, J = 6.8, 3.4 Hz, 1H), 1.84-1.70 (m, 1H), 1.19 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H), 0.53 (d, J = 6.8 Hz, 3H).

Example 12: (4*R*)-4-Isopropyl-5,5-diphenyl-(*N*)-[2-((1*S*, 3*R*, 6*S*)-3-(4-methoxyphenyl)-6-methyl-2,4-dioxacyclohex-1-yl)-(2*R*)-propionyl]-oxazolidin-2-one

A solution of 9.20 g of the diol of Example 6 (21.6 mmol) in 150 mL of CH_2Cl_2 at ambient temperature is treated sequentially with 2.8 g of amberlyst 15 and 4.83 g of anisaldehyde dimethyl acetal (24.9 mmol, 1.22 eq.). The resulting reaction mixture is stirred for 2.5 h, after which it is filtered. The filtrate is concentrated *in vacuo* to give the desired acetal as a crude residue.

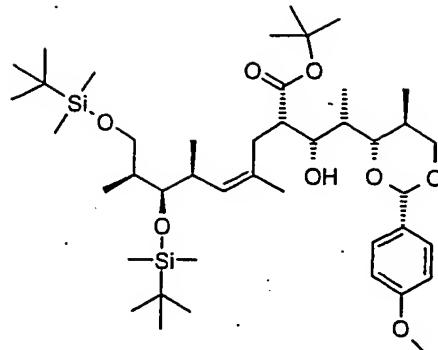
Example 13: (3*R*, 4*R*)-3-hydroxy-4-((1*S*, 3*R*, 6*S*)-3-(4-methoxyphenyl)-6-methyl-2,4-dioxacyclohex-1-yl)-valeric acid *tert*-butyl ester

To a solution of 825 μL of diisopropylamine (5.84 mmol, 2.9 eq.) in 13 mL of a mixture of THF/HMPA (85:15 v/v) at 0 °C under an atmosphere of argon is added 3.65 mL of BuLi (1.6 M in hexanes, 5.8 mmol, 2.9 eq.). After 15 min at 0 °C, the reaction mixture is cooled to -78 °C and treated with 810 μL of *tert*-butyl acetate (6.0 mmol, 3.0 eq.). After 30 min at -78 °C, the reaction mixture is treated by dropwise addition over a period of 10 min with a solution of 529 mg of the aldehyde of stage 13.2 (2.00 mmol) in 9 mL of THF/HMPA (85:15 v/v). After 15 min at -78 °C, the reaction mixture is poured onto 40 mL of sat. aqu. NH_4Cl . The aqu. layer is extracted with TBME (3 x 40 mL). The combined organic layers are washed with sat. aqu. NH_4Cl (30 mL), sat. aqu. NaCl (30 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. After purification by FC (SiO_2 , hexane/AcOEt 4:1), the title compound is obtained as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz, 300K, mixture of epimers, ratio = 3:1) major epimer: δ 7.37 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.47 (s, 1H), 4.26-4.19 (m, 1H), 4.09 (dd, J = 11.3, 4.7 Hz, 1H), 3.78 (s, 3H), 3.70 (dd, J = 10.0, 2.0 Hz, 1H), 3.51 (t, J = 11.1 Hz, 1H), 2.51 (dd, J = 15.5, 8.2 Hz, 1H), 2.39 (dd, J = 15.5, 5.0 Hz, 1H), 1.98-2.17 (m, 1H), 1.92-1.78 (m, 1H), 1.44 (s, 9H), 1.04 (d, J = 7.1 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H); minor epimer: δ 7.34 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 5.48 (s, 1H), 4.08 (dd, J = 11.3, 4.7 Hz, 1H), 4.06-3.97 (m, 1H), 3.91 (dd, J = 10.1, 1.8 Hz, 1H), 3.79 (s, 3H), 3.52 (t, J = 11.1 Hz, 1H), 2.58 (dd, J = 16.0, 3.8 Hz, 1H), 2.39 (dd, J = 16.0, 8.7 Hz, 1H),

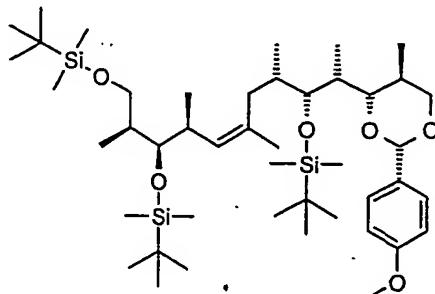
1.98?2.17 (m, 1H), 1.92-1.78 (m, 1H), 1.45 (s, 9H), 0.99 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); MS (EI) m/z 783 (5, $[2 M + Na]^+$), 403 (100, $[M + Na]^+$), 347 (25, $[M + Na - C_2H_8]^+$).

Stage 13.1: To a solution of 12.62 g of the crude acetal of Example 11 in 60 mL of THF at -78 °C under an atmosphere of argon is added over a period of 30 min 62 mL of a 1 M solution of LiAlH₄ in THF (62 mmol). After 3 h of stirring at -78 °C, the reaction mixture is warmed to 0 °C and treated sequentially with 2.4 mL of water, 2.4 mL of 15% aqu. NaOH, and 7.1 mL of water. The resulting precipitate is removed by filtration and washed with THF (2 x 10 mL). The filtrate is collected and concentrated *in vacuo* to half of its initial volume. A white precipitate is formed during the concentration. Heptane (100 mL) is added and more of the precipitate is formed. The suspension is evaporated *in vacuo* to half of its initial volume, stirred at 0 °C for 30 min and filtered. The residue is washed with heptane (3 x 10 mL). The filtrate is collected and concentrated *in vacuo* to give the crude desired alcohol as a yellowish oil.

Stage 13.2: A solution of 3.10 g of oxalyl chloride (24 mmol) in 40 mL of CH₂Cl₂ at -78 °C under an atmosphere of argon is treated sequentially by dropwise addition of a solution of 4.22 g of DMSO (54 mmol) in 16 mL of CH₂Cl₂ and a solution of the crude alcohol of stage 13.1 (6.20 g) in 30 mL of CH₂Cl₂. The resulting reaction mixture is stirred at -78 °C for 30 min. The reaction mixture is then treated by dropwise addition of 18.5 mL of diisopropyl-ethylamine (108 mmol) and is stirred at -78 °C for 1 h before being warmed to 0 °C. Water (70 mL) is added and the aqu. layer is extracted with CH₂Cl₂ (2 x 40 mL). The combined organic layers are washed with sat. aqu. NaCl (2 x 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. After purification by FC (SiO₂, heptane/AcOEt 3:1), the desired aldehyde is obtained as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz, 300K) δ 9.76 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.48 (s, 1H), 4.15 (dd, J = 11.3, 4.7 Hz, 1H), 4.07 (dd, J = 10.1, 2.50 Hz, 1H), 3.79 (s, 3H), 3.58 (dd, J = 11.3 Hz, 1H), 2.58 (qd, J = 7.1, 2.5 Hz, 1H), 2.10 (ddqd, J = 11.3, 10.1, 6.7, 4.7, Hz, 1H), 1.24 (d, J = 7.1 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H).

Example 14:

To a stirred solution of LDA (0.71 mmol, prepared from 0.77 mmol of diisopropylamine and 0.71 mmol of BuLi 1.6 M in hexanes at 0 °C) in THF (0.30 mL) at -50 °C under an atmosphere of argon is added a solution of the product from Example 13 (118 mg, 0.31 mmol) in THF (0.30 mL). The reaction mixture is allowed to warm to -10 °C and stirred at that temperature for 10 min. The reaction mixture is then cooled to -50 °C and stirred at that temperature for 30 min. A solution of the product from stage 8.4 (244 mg, 0.42 mmol) in a mixture of THF (0.10 mL) and HMPA (0.10 mL) is added. The reaction mixture is stirred for 2 h at -50 °C before being diluted with TBME (2 mL) and poured into an aqu. sat. solution of NH₄Cl (2 mL). The reaction mixture is then partitioned between NaHCO₃ (2 x 5 mL) and TBME (2 x 5 mL). The combined organic extracts are washed with NaCl (5 mL), dried (MgSO₄) and concentrated *in vacuo*. Filtration over SiO₂ (5% EtOAc/Hexanes) provides the product as a colourless oil; MS (EI) *m/z* 801 (100, [M + Na]⁺).

Example 15:

To a stirred solution of the crude product of stage 15.3 (350 mg, 0.39 mmol) in THF (10 mL) at -78°C is added LiAlH₄ (4.0 mL of a 1M/THF solution, 4.00 mmol) and allowed to gradually warm to -10°C over 1.5 h. The reaction is then quenched by the addition of MeOH (2 mL) and partitioned between potassium sodium tartrate (15 mL) and TBME (3 x 50 mL). The combined organic extracts are dried (MgSO₄) and concentrated *in vacuo*. Flash chromatography (95% EtOAc/hexane) gives the desired compound as a colourless solid; IR (KBr): ν_{max} 2959s, 2930s, 2857s, 1472m, 1462m, 1250s, 1113m, 1083s, 1062s, 1038m, 1019s, 1005w, 856w, 835s, 774s; ¹H-NMR (CDCl₃, 500 MHz, 298K) δ 7.85 (dt, *J* = 9.0, 2.0 Hz, 2H), 6.88 (dt, *J* = 9.0, 2.0 Hz, 2H), 5.39 (s, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 4.10 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 5.0, 2.0 Hz, 1H), 3.62 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.52 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.48 (t, *J* = 11.5 Hz, 1H), 3.43 (t, *J* = 5.5 Hz, 1H), 3.36 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.51 (m, 1H), 2.34 (t, *J* = 12.0 Hz, 1H), 2.06 (m, 1H), 1.99 (m, 1H), 1.88 (td, *J* = 7.0, 1.5 Hz, 1H), 1.80 (m, 1H), 1.71 (br d, *J* = 11 Hz, 1H), 1.58 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (d, *J* = 7 Hz, 3H), 0.889 (s, 9H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.50 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 9H), 0.01 (s, 3H); ¹³C-NMR (CDCl₃, 125 MHz, 300K) δ 131.8, 131.7, 127.5, 114.5, 113.6, 101.2, 83.6, 78.6, 77.7, 73.5, 65.5, 55.4, 41.5, 38.3, 37.5, 35.4, 34.0, 31.0, 26.1, 26.0, 25.8, 23.3, 18.6, 18.5, 16.8, 13.8, 12.8, 12.3, 11.0, 5.9, -3.3, -3.4, -3.5, -3.6, -3.8, -5.1; MS (EI) *m/z*: 829 (7, [M+Na]⁺), 826 (17, [2M +Ca]²⁺), 377 (90), 313 (100).

Stage 15.1: To a stirred solution of the crude product of Example 14 (400 mg, 0.51 mmol) in CH₂Cl₂ (10 mL) at -78°C Et₃N (714 μL, 5.13 mmol) is added, followed by addition of TBDMsOTf (586 μL, 2.55 mmol). The reaction mixture is allowed to warm to RT and stirred for 4 h. The reaction mixture is then partitioned between NaHCO₃ (20 mL) and CH₂Cl₂ (3 x 50 mL). The combined organic extracts are dried (MgSO₄) and concentrated *in vacuo*. Filtration over SiO₂ (5% EtOAc/Hexanes) gives the crude product as a colourless oil; MS (EI) *m/z* 915 (100, [M + Na]⁺).

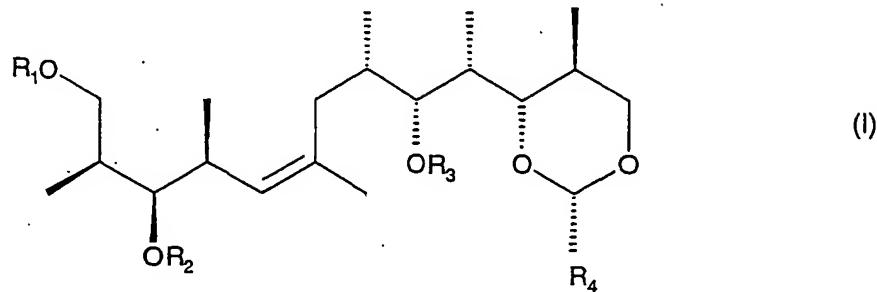
Stage 15.2: To a stirred solution of the crude product of stage 15.1 (561 mg, 0.63 mmol) in THF (15 mL) at -78°C is added LiAlH₄ (6.30 mL of a 1M/THF solution, 6.30 mmol). The reaction mixture is allowed to gradually warm to -15°C over 1 h. The reaction mixture is then quenched by the careful addition of a aqu. solution of potassium sodium tartrate (30 mL) and stirred vigorously at RT. After 30 min, the layers are separated and the aqu. layer is extracted with TBME (3 x 100 mL). The combined organics are dried (Na₂SO₄) and

concentrated *in vacuo*. Filtration over SiO_2 (5-30% EtOAc/Hexanes) provides the desired alcohol as a colourless oil; MS (EI) m/z 923 (100, $[\text{M} + \text{Na}]^+$).

Stage 15.3: To a stirred solution of the crude product of stage 15.2 (400 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) at RT is added Et_3N (338 μL , 2.43 mmol) and methanesulfonylchloride (58 μL , 0.74 mmol). After 20 h the mixture is partitioned between NaHCO_3 (15 mL) and CH_2Cl_2 (3 x 20 mL). The combined organic extracts are dried (Na_2SO_4) and concentrated *in vacuo*. Filtration over SiO_2 (10-20% EtOAc/Hexanes) gives the crude product as a colourless oil; MS (EI) m/z 891 (100, $[\text{M} + \text{Na}]^+$).

WHAT IS CLAIMED IS:

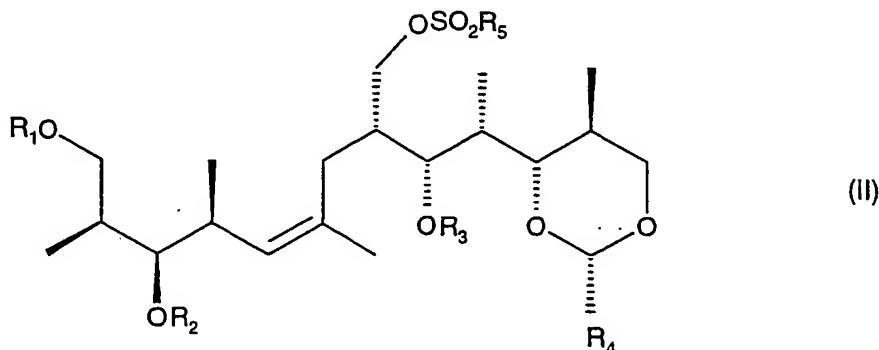
1. A process for preparing a substituted alkene of formula I



wherein

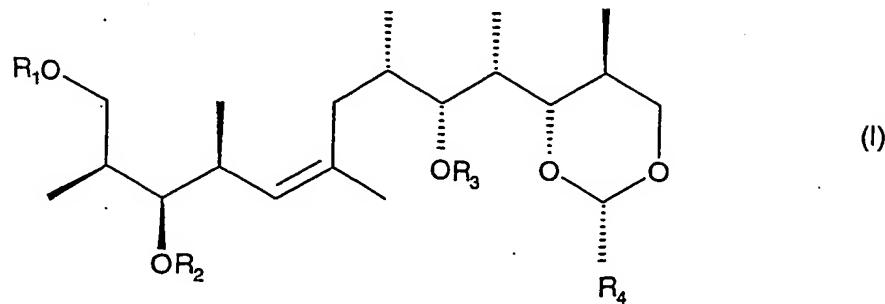
R₁, R₂ and R₃ are independently of each other a protecting group for a hydroxy group or hydrogen and

R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, in which process a sulfonate of formula (II),



wherein R₁, R₂ and R₃ are all protecting groups for a hydroxy group which protecting groups can be identical or different, R₄ has the meaning as defined for the compound of formula I and R₅ is alkyl or aryl which is unsubstituted or substituted by alkyl, is reduced and afterwards, if desired, one, two or all protecting groups R₁, R₂ and R₃ are split off.

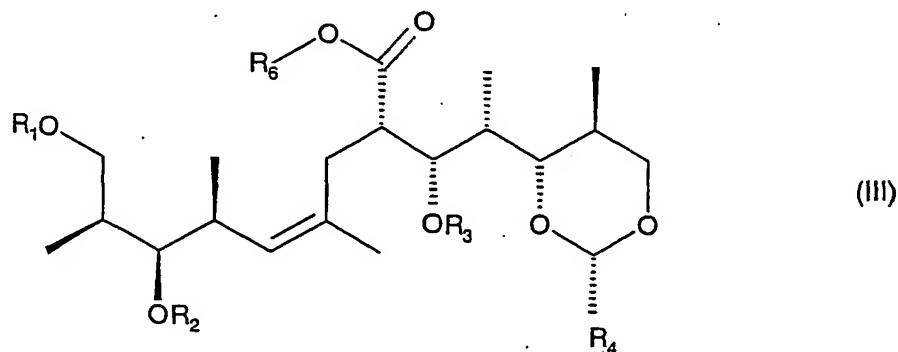
2. A process for preparing a substituted alkene of formula I



wherein

R_1 , R_2 and R_3 are independently of each other a protecting group for a hydroxy group or hydrogen and

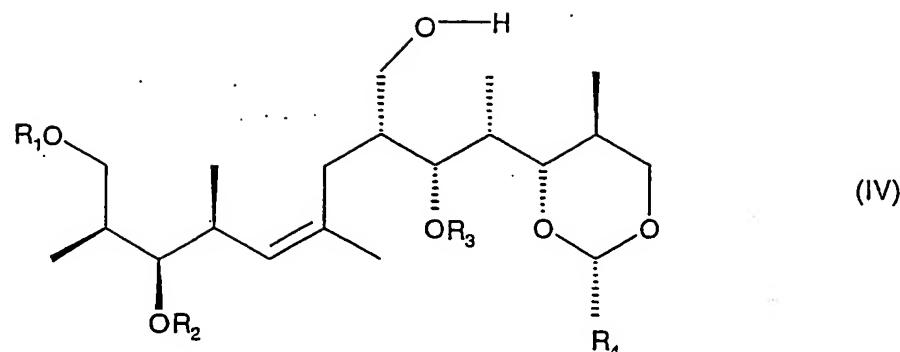
R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, in which process a carboxylic ester of the formula III



wherein R_1 , R_2 and R_3 are all protecting groups for a hydroxy group which protecting groups can be identical or different, R_6 is alkyl or arylalkyl, and R_4 has the meaning as defined for the compound of formula I,

is first reduced, the obtained alcohol of the formula IV

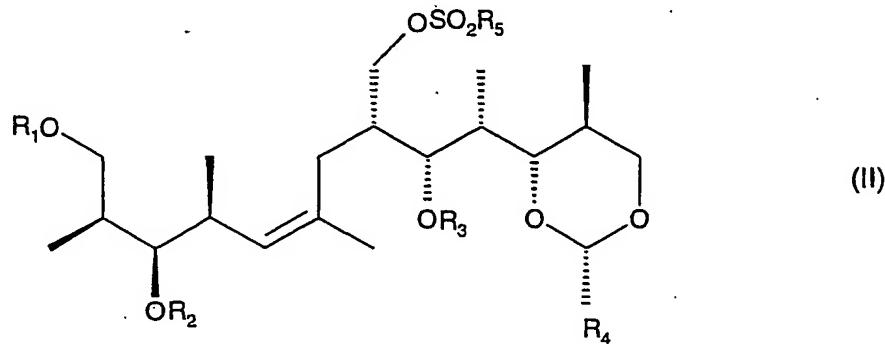
- 40 -



wherein R_1 , R_2 , R_3 and R_4 have the meanings as defined for the compound of formula III, is further reacted with a compound of formula V



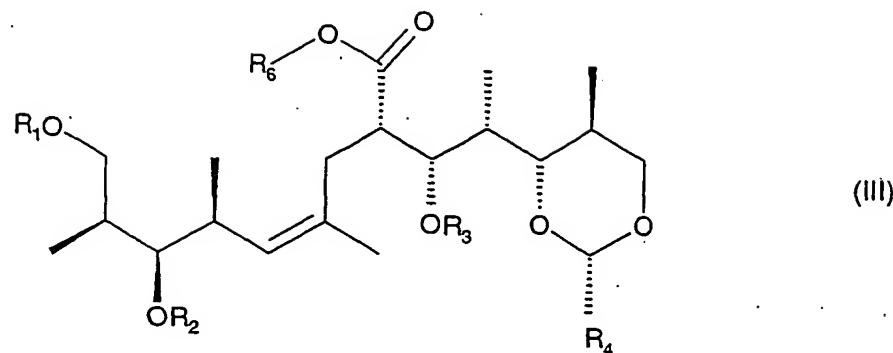
wherein R_5 is alkyl or aryl which is unsubstituted or substituted by alkyl, and Hal represent halogen, and the obtained sulfonate of formula II



wherein

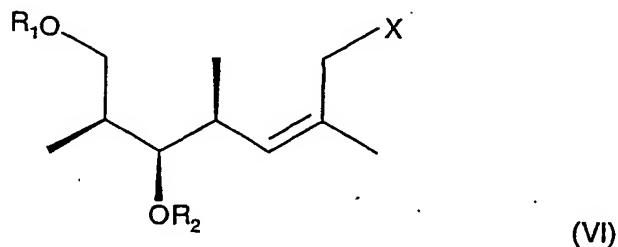
R_1 , R_2 , R_3 and R_4 have the meanings as defined for the carboxylic ester of formula III and R_5 is alkyl or aryl which is unsubstituted or substituted by alkyl, is further reduced, and, if desired, one, two or all protecting groups R_1 , R_2 and R_3 are detached by methods known in the art.

3. A process for preparing a carboxylic ester of formula III



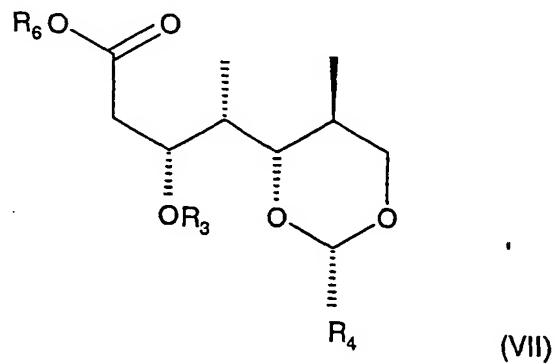
wherein

R_1 and R_2 are protecting groups for a hydroxy group which protecting groups can be identical or different or hydrogen, R_3 is hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl,
in which process an allyl halide of the formula VI



wherein R_1 and R_2 have the meanings as defined for a carboxylic ester of formula III and X is halogen,

is reacted with a carboxylic ester of formula VII

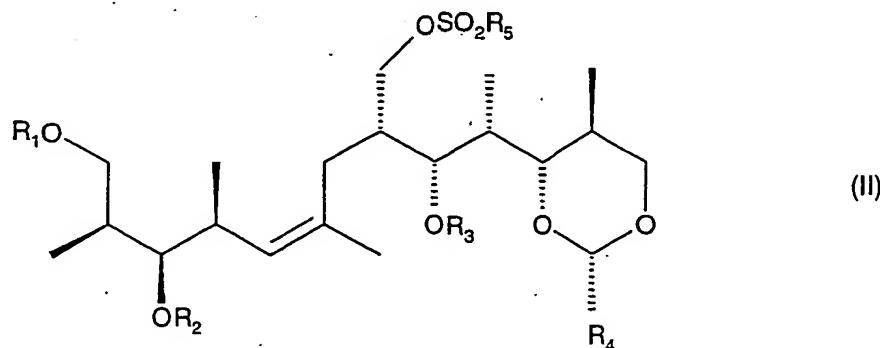


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wherein R_3 , R_4 and R_6 have the meanings as defined for a carboxylic ester of formula III in the presence of a base,
and afterwards, if desired, one or all protecting groups R_1 and R_2 are split off.

4. A process according to any one of claims 1, 2 or 3 wherein R_1 and R_2 are identical and R_1 , R_2 and R_3 are silyl protecting groups.

5. A sulfonate of formula II

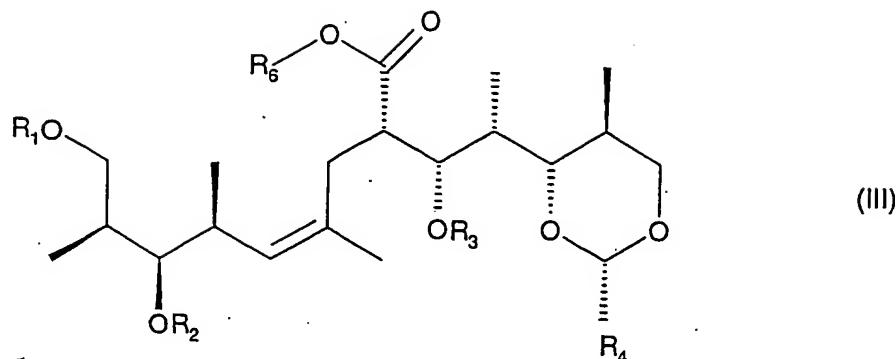


wherein R_1 , R_2 and R_3 are all protecting groups for a hydroxy group which protecting groups can be identical or different, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_5 is alkyl or aryl which is unsubstituted or substituted by alkyl.

6. A sulfonate of formula II according to claim 5 wherein R_1 and R_2 are identical, R_1 , R_2 and R_3 are benzyl or silyl protecting groups, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_5 is lower alkyl or phenyl which is substituted by lower alkyl.

7. A sulfonate of formula II according to claim 5 wherein R_1 and R_2 and R_3 are *tert*-butyl dimethylsilyl, R_4 is phenyl which is unsubstituted or monosubstituted by lower alkoxy and R_5 is lower alkyl or phenyl which is monosubstituted by lower alkyl.

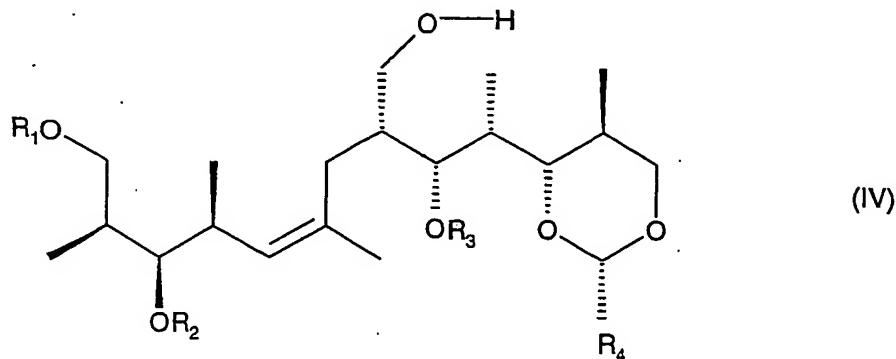
8. A carboxylic ester of formula III



wherein R_1 and R_2 are protecting groups for a hydroxy group which protecting groups can be identical or different, R_3 is a protecting group for a hydroxy group or hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl.

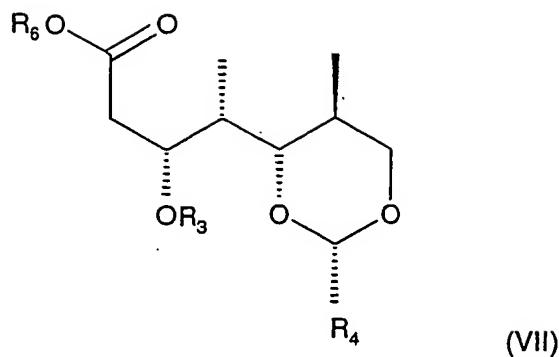
9. A carboxylic ester of formula III according to claim 8 wherein R_1 and R_2 are identical, R_1 , R_2 and R_3 are silyl protecting groups and R_6 is lower alkyl.

10. An alcohol of formula IV



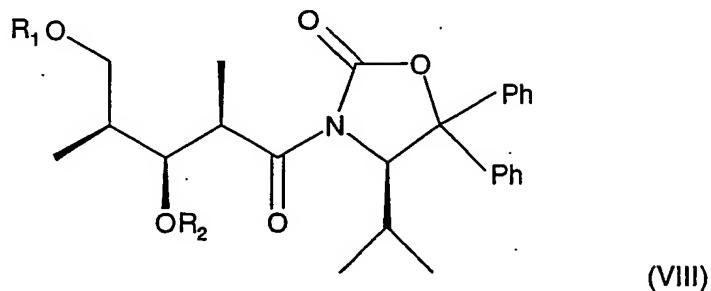
wherein R_1 , R_2 and R_3 are all protecting groups for a hydroxy group which protecting groups can be identical or different and R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy.

11. A carboxylic ester of formula VII



wherein R_3 is hydrogen, R_4 is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, and R_6 is alkyl or arylalkyl.

12. An oxazolidinone of formula VIII



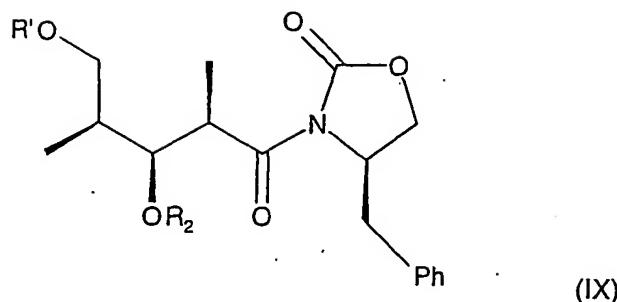
wherein

Ph denotes phenyl, and

R_1 and R_2 are independently of each other a silyl protecting group, hydrogen or benzyl which is unsubstituted or mono- or disubstituted by lower alkoxy, or

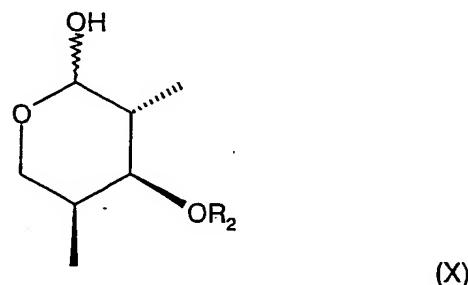
R_1 and R_2 together represent methyliden substituted by phenyl which phenyl group is mono- or disubstituted by lower alkoxy.

13. An oxazolidinone of formula IX



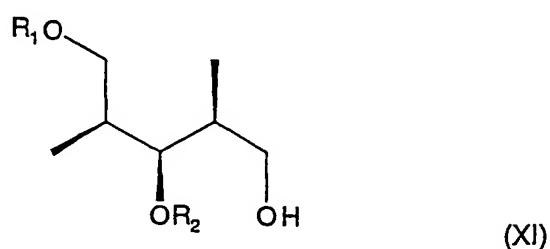
wherein Ph denotes phenyl, and R' and R_2 are independently of each other a silyl protecting group, hydrogen or benzyl which is unsubstituted or mono- or disubstituted by lower alkoxy under the proviso that one of both radicals R' and R_2 is a silyl protecting group.

14. A δ -valerolactol of the formula X



wherein R_2 is a protecting group for a hydroxy group.

15. An alcohol of the formula XI

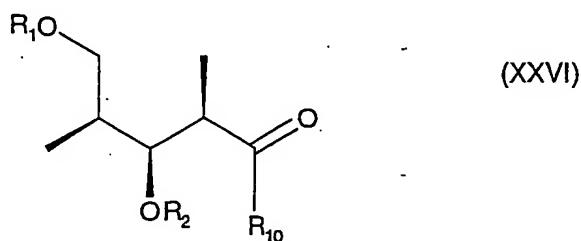


wherein both R_1 and R_2 represent a silyl protecting group.

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16. The use of a sulfonate of formula II according to any one of claims 5 to 7, of a carboxylic ester of formula III according to claim 8 or 9, of an alcohol of formula IV according to claim 10 or a carboxylic acid according to claim 11 in a process for the manufacture of discodermolide or discodermolide analogues.

17. A process for preparing an ether of formula XXVI



wherein

R₁ is benzyl which is mono- or disubstituted by alkoxy,

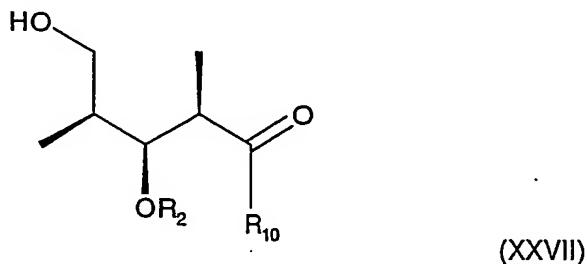
R₂ represents a protecting group for a hydroxy group or hydrogen and

R₁₀ is N-oxazolidinyl which is unsubstituted or substituted by alkyl, benzyl or phenyl;

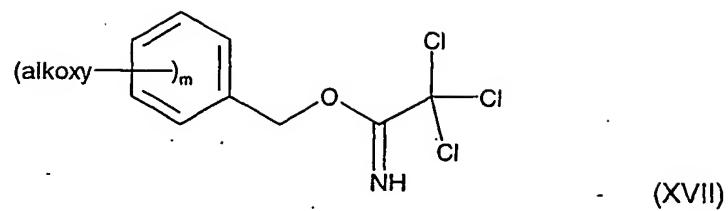
OR₆ wherein R₆ is alkyl or benzyl, or

N(R_a)₂ wherein R_a is alkyl or benzyl,

characterized in that a compound of formula XXVII,



in which the radicals R₂ and R₁₀ are as defined for the compound of formula XXVI, is reacted with a trichloroacetimidate of formula XVII



wherein m is 1 or 2, in the presence of samarium triflate or ytterbium triflate, and afterwards, if desired, the protecting group R₂ is split off.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
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(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(21) International Application Number: PCT/EP02/00570

(22) International Filing Date: 21 January 2002 (21.01.2002)

(25) Filing Language: English

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(30) Priority Data:
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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.

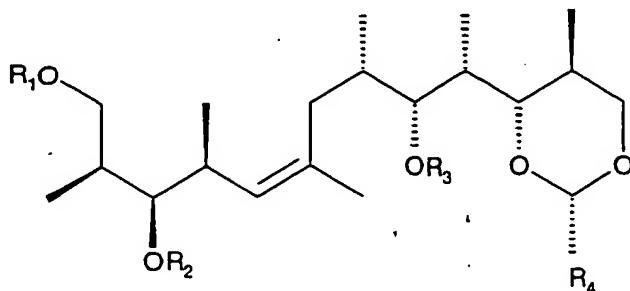
(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— with international search report

(88) Date of publication of the international search report: 10 October 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING INTERMEDIATES FOR THE MANUFACTURE OF DISCODERMOLIDE AND DISCODERMOLIDE ANALOGUES



WO 02/057251 A3

(57) Abstract: The invention relates to a process for the preparation of a substituted alkene of formula (I) wherein R₁, R₂ and R₃ are independently of each other a protecting group for a hydroxy group or hydrogen and R₄ is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, which alkene constitutes an intermediate for the preparation of discodermolide and discodermolide analogues.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00570

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D319/12 C07D263/26 C07D309/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BURKE ET AL.: "An alternative route to the C(7)-C(13) subunit of erythronolide B via a hydropyran template" TETRAHEDRON LETT., vol. 28, no. 36, 1987, pages 4147-4148, XP001062534 reaction of compound 12 to compound 13, step (p)	1,4-7, 10,16
Y	reaction of compound 12 to compound 13, step (n)	2,4-7, 10,16
	----	-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

5 July 2002

17.07.02

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAGASAWA K ET AL: "Total Synthesis of Preswinholide A. 2. Completion of the Synthesis" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 38, 16 September 1996 (1996-09-16), pages 6885-6888, XP004030775 ISSN: 0040-4039 scheme, reaction step g page 6886	2,4-7, 10,16
A	A. B. SMITH III ET AL.: "Evolution of a Gram-Scale Synthesis of (+)-Discodermolide" J. AM. CHEM. SOC., vol. 122, - 26 August 2000 (2000-08-26) pages 8654-8664, XP002194754 cf. scheme 9	3,8,9,11
A	FILLA S A ET AL: "Synthesis of C1-C8 and C9-C24 fragments of (-)-discodermolide: use of asymmetric alkylation and stereoselective aldol reactions" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 40, no. 30, July 1999 (1999-07), pages 5449-5453, XP004171484 ISSN: 0040-4039 cf. scheme 4 (reaction of 9b to 11)	3,8,9,11
A	SMITH A B ET AL: "TOTAL SYNTHESIS OF (-)-DISCODERMOLIDE" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 117, 1995, pages 12011-12012, XP001018841 ISSN: 0002-7863 cf. scheme 6	3,8,9,11
A	WO 98 48791 A (YANG GE ;MYLES DAVID C (US); HARRIED SCOTT S (US); UNIV CALIFORNIA) 5 November 1998 (1998-11-05) Figure 3, compound 15, abstract the whole document	1-14,16, 17
A	US 5 789 605 A (KOBAYASHI KAORU ET AL) 4 August 1998 (1998-08-04) Figure 3, compound (+)-10 abstract	12-14,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/00570

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 15 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 15

The following stated with regard to the second invention, i.e. claims 12-15, 17:

In the case of claim 15 the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of this claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Consequently, the search has been restricted to claims 12-14 and 17.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11,16

Process for the preparation of (I), intermediates/precursors taking part in this process and the usage of the intermediates therein

2. Claims: 12-15,17

Intermediates in the process for the preparation of discodermolide and analogues thereof, an process for the preparation of these intermediates and intermediates of these intermediates.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/00570

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9848791	A 05-11-1998	AU 7267298 A	WO 9848791 A1	24-11-1998 05-11-1998
US 5789605	A 04-08-1998	EP 0969829 A1	JP 2001515466 T	12-01-2000 18-09-2001
		US 6031133 A	WO 9824429 A1	29-02-2000 11-06-1998
		US 6096904 A	US 6242616 B1	01-08-2000 05-06-2001

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